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Internal Secretions from a Physiological and Therapeutical Standpoint

BY

ISAAC OTT, A.M., M.D.

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Preface

These three lectures were delivered before the students of the Medico-Chirurgical College. Owing to the many requests for several parts of our various publications of the work done in the laboratory I have thought it best to incorporate the results in a general review of the internal secretions. While many statements are contradictory, yet I have included them, as the whole subject is in a stage of flux and reflux. "Dire n'est rien; faire est tout"—*Renan.*

ISAAC OTT.

Sept. 28, 1910.

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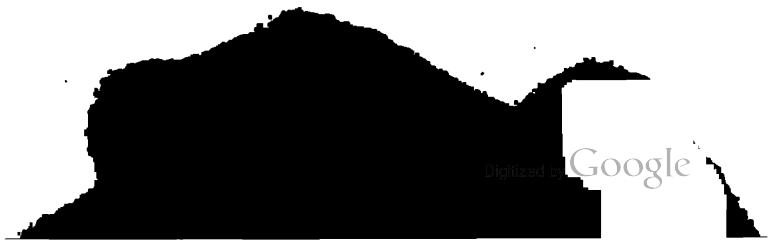
FIRST LECTURE.—THE PARATHYROIDS.[1]

Gentlemen: I have great pleasure in extending you a hearty greeting to a renewal of our studies in the Physiology of the second year. Your extensive laboratory course has well fitted you to understand the lectures of this semester. I have chosen to-day as a subject the parathyroid glands. Dr. Scott and I have devoted the past year to a study of these glandules. In my remarks about them I shall keep close to the facts and not to theory, for Venturi in the 15th century very wisely stated: "Theory is the general, experiments are the soldiers. The interpreter of the artifices of nature is experience. She is never deceived. Our judgment sometimes is deceived because it expects effects which experience refuses to allow." In another place, in reference to a particular case, Venturi states that Nature begins from the Reason and ends in Experience, but for all that we must take the opposite course, begin from the Experiment and try to discover the Reason.

There is no field in Physiology where more theories can be heralded than about the glands with an internal secretion. I shall preface the lecture by calling your attention to some of the discoveries about internal secretions

[1] Introductory lecture delivered at the opening of the course on Physiology at the Medico-Chirurgical College of Philadelphia, 1909-'10, by Isaac Ott, M.D.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in the laboratory of our college. It was the genial Franco-American physiologist, Brown-Sequard, who in 1856 first stated that the adrenals when removed caused the death of the animal. This was the commencement of the discoveries about glands with an internal secretion.

I was the first to state, in the *Medical Bulletin*, 1897, that "the adrenals enlarged the lumen of the intestine at the moment of the injection of the filtrate. When the arterial tension is mounting the intestine is relaxing."

This property of the adrenal is of value in intestinal hemorrhage of typhoid fever in slowing the peristalsis. In the same paper I showed that the spleen had a most marked effect in exciting peristaltic movements. I have also shown in the laboratory that iodothyrin excites peristalsis and explains the diarrhea in exophthalmic goitre, where we usually have a hyperthyroidism. We also found that the mammary, prostate and spermin were powerful excitants of uterine contraction.

The parathyroids were first discovered by Sandstroem, a Swedish anatomist, in 1880. They are often called by the Germans, epithelial bodies (Epithelkoerper).

Parathyroids, Position of.—In the cat the parathyroids are very regularly four in number, two on each lobe; an external one more or less free upon the external surface of the thyroid, and an internal one embedded in the substance of the lobe nearer to the internal than the ex-

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ternal surface of the thyroid, and always smaller than the external. From their anatomical position the cat is the most suitable animal for parathyroidectomy. In color and size they resemble in the cat miliary tubercles.

The rabbit has two thyroid lobes connected by an isthmus. In each lobe is embedded a parathyroid. Two additional parathyroids, one on each side, lie distinct from the thyroid, usually at some distance from it. He has four parathyroids.

In the dog there are four parathyroids, but the external pair are usually embedded in the thyroid. The internal parathyroids are rarely seen exposed upon the internal surface of the thyroid.

Guinea Pig.—The thyroids usually consist of two separate and distinct lobes, with occasionally an isthmus uniting the lower ends of the lobes. The number and position of the parathyroids is variable, more so than in any other animal. Each lobe of the thyroid contains a parathyroid embedded more or less in its tissue; besides these, two additional parathyroids on each side separated from the thyroid and variable in position in the levels of the thyroids. He has four parathyroids.

Rats.—The thyroid consists of two lobes united by an isthmus, one parathyroid to each lobe, lying on the external surface. ' It is easily accessible and can be readily cauterized.

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In the monkey there are four parathyroids, always embedded in the substance of the thyroid, two in each lobe.

In man, the parathyroids are three or four in number, two on each side in front of the vertebral column just behind the rear margins of the lateral lobes of the thyroid gland. The inferior thyroid artery is in close relation with them. A small grain of Indian corn represents their size and shape. Their color is reddish yellow or reddish brown (Fig. 1).

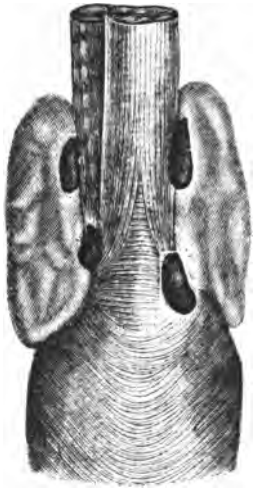

FIG. 1.—The Four Parathyroids in Man—Posterior View (Zuckerkandl).

Gilbride, in man, found that the most common site of the parathyroids is in the region of the inferior poles of the thyroid gland; the superior

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or external glands are behind and close to the inferior border of the lateral lobes and in close proximity to the inferior thyroid artery, the inferior or internal glands lying posterior and below the superior glands, nearer the median line or below the thyroid and resting on the anterior and lateral surface of the trachea.

W. Berkeley, in 125 autopsies, occasionally found as many as five or six, often only two or three, but always one, parathyroid.

Proportion of Parathyroid to That of the Thyroid.—Thyroid tablets of commerce are chiefly from the glands of the lamb. The fresh thyroids of six mature lambs weighed 24.7 grams (dried 8.4 grams), while twelve external parathyroids, fresh, weighed 0.23 gram (dried 0.09 gram). In feeding with thyroid tablets the parathyroids play an exceedingly small part in the medication.

Histology.—These glands are rich in cellular elements and enclosed by a delicate capsule of connective tissue. In the parathyroid, trabeculae run from the deep surface of the enveloping capsule, branch and unite to divide the interior of the gland into polygonal compartments. The cells are small, with a large round nucleus. The amount of protoplasm in the cell is small. The cells of the parathyroid are in structure very different from those of the thyroid. The cells are of two types, the chief and oxyphile, which are considered by Forsythe to represent two stages in the activity of one kind of

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cell. In repose, the clear protoplasm of the chief cells are filled with oxyphile granules which are subsequently extruded, and run together to form drops of colloid material which enters the blood *via* the lymphatics.

In the parathyroids the masses of polyhedral cells are in varying stages of active secretion; often, however, a drop of the colloid secretion forces the cells apart. The formation of vesicles in the isolated parathyroid is quite common in the glands of man.

Morphology.—Three diverticula form the thyroid, a median one growing from the second visceral arch and which moves to a pretracheal position, where it is connected with the lateral thyroid buds which develop from the dorsal wall of the fourth inner pharyngeal cleft.

Parathyroids are thickenings of the epithelium on the dorsal aspect of the third and fourth visceral clefts. The thymus arises as a pair of outgrowths from the epithelium of the third cleft.

Chemistry of the Parathyroids.—The colloid material secreted by the parathyroid is now conceded not to contain iodine. Glycogen is found in abundance.

Blood Supply.—The parathyroids receive their blood supply usually from the inferior thyroid artery. Nate Ginsburg has shown that one of the superior parathyroids derives its blood supply from the superior parathyroid artery instead of from the inferior thyroid artery.

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Ginsburg also found that there is an anastomosis between the parathyroid arteries on one side with those of the other, so if one of the inferior or superior thyroid arteries is intact the blood supply not only of the parathyroid bodies of one side, but those on the other, are preserved.

Parathyroids in Thymus.—Erdheim found small accessory parathyroid glandules in the thymus. This has also been seen by Pepere in rabbits and in man. Harvier and Morel[1] found in half of the cases a group of parathyroids in the cat, chiefly in the cervical lobes. They found that tetany did not ensue unless these thymic parathyroids were also removed. Dr. Scott and I have frequently noted and removed the thymic parathyroids.

Changes in Parathyroids after Removal of Thyroids.—When the thyroids were removed it was found, by Vincent and Jolly, that the parathyroid tissue approximates in appearance to ordinary thyroid tissue. There is, however, no hypertrophy of the tissues of the parathyroids.

Walter Edmunds[2] has shown by experiments upon dogs that the parathyroids even when left in animals with great thyroid insufficiency do not change into thyroid proper.

What is Tetany?—This name "tetanie" was first used by Lucien Vavirsort in 1852. It is not a distinct disease, but a symptom-complex. It consists of spontaneous intermittent muscular contractions, attended with decreasing strength

[1] *Comptes Rendus de la Biologie*, May, 1909, p. 837.
[2] *Journal of Pathology and Bacteriology*, 1910, p. 288.

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until death ensues. There is also a spastic, tottering gait, tachycardia, dyspnea, rapid emaciation and psychical depression. It is associated with hypoparathyroidism.

When all the parathyroids are removed there is partial paralysis, especially of the extensors; trembling in all the muscles, followed by a series of convulsive attacks, with loss of appetite; there is often vomiting and dyspnea, which is replaced by polypnea during the convulsive attack. The temperature rises during the convulsions, which fact we have often observed. This tetany begins in twenty-four to forty-eight hours after the operation in the dog and cat. The dog generally dies from the second to the fifth day in convulsions. Robert Quest, in 1905, analyzed the brains of three infants dead by tetany and found the amount of calcium to be small. There was also a change in the proportion between the amount of sodium to that of calcium.

Oddo and Sarles found the urine in the tetany of infants to have an exaggerated amount of calcium phosphates. They explained the cause of tetany to be due to loss of calcium salts. Silvestri (1906) held that tetany and eclampsia could be explained by a diminution of the calcium in the organism.

Netter cured three cases of tetany in infants with calcium chloride by the mouth. MacCallum and Voegtlin confirmed the results of

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Quest as to the lessened amount of calcium in the brain. They also confirmed the results of Oddo and Sarles that there was an increased excretion of calcium in the urine. MacCallum and Voegtlin also found the calcium content in the muscles and blood to be one-half the usual amount. Halstead has cured tetany in man, due to the removal of the parathyroids in operations on the thyroid, by calcium.

MacCallum and Voegtlin arrested tetany for twenty-fours hours in dogs when seven grains of calcium lactate were given by the vein. Beebe has shown that injection of parathyroid extract causes the symptoms of tetany to vanish for a time, but death finally ensued, just as it did in animals after the use of calcium lactate.

Quantity of Calcium.—Parhon, Dumitresco and Nissipesco[1] found that in proportion to weight, animals, cats chiefly and dogs, the proportion of calcium in the nerve centers was greater after thyroparathyroidectomy than in normal animals. They do not confirm Silvestri and MacCallum's results.

Leopold and V. Reuss[2] in rats after removal of the parathyroids found rather an increase of calcium in the body when compared with normal animals. These experiments would rather support the theory of Stoelzner, that there is a hypercalcification which causes tetany.

Quest made some experiments upon dogs

[1] *Comptes Rendus de la Société de Biologie*, 1909, May, p. 792.
[2] *Wiener Klin. Wochenschrift*, No. 35, 1908, p. 1243.

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by subcutaneous injection of calcium chloride solution to produce an excess of calcium in the body. He never observed an elevation of the electric excitability of the nerves. The faradic current showed a prompt depression of irritability.[1] These experiments tend to prove that Stoltzner's idea that an excess of calcium causes tetany is not correct.

Musser and Goodman[2] studied the metabolism of a case of surgical or post-operative tetany. They found no "diabetes calcareus," but a marked diminution of the calcium in the urine. They found no relation between the amount of calcium and the severity of the symptoms. They pertinently ask: If tetany is due to a withdrawal of calcium, why should the symptoms persist when the organism is in the perpetual condition of calcium store? Leopold and Von Reuss suggest that the poison which normally is paralyzed by the parathyroids is able to precipitate calcium and leads to the deprivation of the organism of active calcium in a physiological sense. This might explain that with normal or increased total calcium there could be a poverty in active calcium.

Musser and Goodman found a high percentage of ammonia in the urine, it never falling below 5 per cent. This coefficient of ammonia bore a distinct relation to tetany. They practically found that when rigidity or some distress ref-

[1] *Berliner Klinische Wochenschrift*, 1910, p. 1074.
[2] *University of Penna. Medical Bulletin*, p. 90, May, 1909.

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erable to the tetany was complained of, the ammonia percentage was raised. They are of the opinion that an acidosis may be the underlying feature of surgical tetany.

MacCallum and Voegtlin have discovered in parathyroidectomized animals: (1) a marked reduction in the calcium content of the tissues, especially of the blood and brain; (2) an increased output of calcium in the urine and feces on the development of tetany; (3) an increased output of nitrogen in the urine; (4) an increased output of ammonia in the urine, with an increased ammonia ratio in the urine; and (5) an increased amount of ammonia in the blood.

Jean V. Cooke[1] found in dogs dying from parathyroid tetany a slightly greater amount of calcium in the brain than in the brain of normal dogs, which indicates that a decreased calcium content of the brain is not constant in tetany. After removal of the parathyroids, with the animal fasting, the elimination in urine of magnesium is greatly increased, while that of calcium remains unchanged. The augmentation of magnesium begins before tetany is observed. It is suggested that tetany represents a condition of altered salt equilibrium in the nerve cells brought about by a disturbance in the catalytic processes of the body which increases the acid factors.

Walter Edmunds[2] found in animals, if a large

[1] *Proceedings of Society for Experimental Biology and Medicine*, 1909, p. 13.

[2] *Journal of Pathology and Bacteriology*, 1910, p. 290.

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amount of calcium was given or mainly fed on milk previous to the operation, that after a total thyroidectomy which includes the parathyroids the symptoms ensuing are removed or temporarily mitigated. The calcium and milk was continued after the operation.

Poison in the Blood of Animals in Tetany.—Pfeiffer and Mayer found in the sera of six out of seventeen dogs, which had tetany after removal of the parathyroids, a toxic principle. This was shown by experiments upon mice.

Berkeley and Beebe regard tetany to be due to a metabolic poison: (1) the symptoms have a central origin; (2) the symptoms are shown best in young animals and are more severe if the animal is kept on a meat diet; (3) the symptoms have a close relation to certain chemical conditions which are accompanied by severe nutritional disturbances; (4) gastric tetany is accompanied by severe metabolic disturbances, it has similar symptoms and is promptly relieved by intravenous injection of calcium and by parathyroid and nucleoproteid; (5) bleeding followed by intravenous infusion relieves the animal, a procedure well suited to free the body from a circulating poison; (6) symptoms are promptly relieved by the injection of fresh parathyroid nucleoproteid; (7) injections of known simple poisons, such as ammonia and xanthin, produce symptoms which can be promptly relieved by injections of calcium or strontium salts similar to the relief obtained

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by the same means in tetany; (8) parathyroid tetany has a deranged metabolism accompanied by a large increase in the excretion of ammonia.

Meljnikow,[1] in tetany of rabbits after removal of parathyroids, found that injections of calcium acetate quickly improved the animals, but it was quite temporary. He states that the parathyroids have a specific histological structure which is not converted into thyroid tissue. Goitre degeneration of the thyroid has but little effect upon the parathyroids. There is some regressive change, probably due to mechanical pressure from the enlarged thyroid, and not to any physiological connection with the thyroid.

Beebe found that strontium acted equally well as calcium in relieving tetany. Barium also relieves tetany. These facts indicate that calcium loss is only a part of the factors in the course of tetany.

Bleeding cures tetany, but it can not do it by loss of calcium, as this operation diminishes this element more. It is not likely in forty-eight hours after the operation that in the onset of tetany the hypocalcification is so great as to cause the disease, for plenty of calcium can come from the store-house in the bones.

Magnesium also relieves tetany, according to MacCallum and Beebe. Neither barium nor magnesium should be used, as they are toxic to the heart. Beebe found parathyroid

[1] *Wiener Klinische Wochenschrift*, 1910, p. 410.

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nucleoproteid to relieve tetany. The globulin in parathyroids has no effect on tetany. The nucleoproteid will relieve tetany if given by the mouth, but is much more quickly and certainly effective when given subcutaneously or intraperitoneally.

Berkeley and Beebe are inclined to believe that the parathyroids are chiefly concerned in furnishing enzymes, which are of prime importance in the intermediary metabolism of nitrogen. They do not believe that the abnormal secretion of calcium is the cause of tetany, but a deranged metabolism giving rise to an active poison.

Clara Jacobson finds in the blood of parathyroidectomized animals an increase of ammonia and she believes it is directly responsible for the tetany, as the concentration of ammonia in the blood of the parathyroidectomized cats and dogs is sufficient to cause tetany, tremors, and depression in the normal animal. Normally in cats it is 1.57 milligrams per 100 cc., but in parathyroidectomized animals it is on an average of 6 animals 2.53.[1]

Our experiments were made upon sixty cats and two dogs. One hundred and thirty-three observations were made on these sixty-two animals. The cats were first etherized, then the parathyroids removed under antiseptic precautions. The thymus was always examined

[1] *Proceedings of Society for Experimental Biology and Medicine*, Vol. VIII, No. 4, p. 124.

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for parathyroids. The cat has usually four parathyroids, but more may exist. In young cats the parathyroids have a looser anatomical relation to the thyroid than later in life. In many cases some of the thyroid was removed in the desire to obtain all the parathyroids, but enough thyroid was left to maintain its functions. When removal in part of the parathyroids was ineffectual to produce a tetany, then the thyroid was also removed, and we always found it contained a parathyroid larger than the normal. In cats, when all the parathyroids were removed symptoms of tetany came on in about forty-eight hours as a rule. The first symptoms were a slowness in movement and a state of apathy. The animals were disposed to remain in one place. First, as a rule, was developed a lifting of the posterior extremities and sometimes of the anterior, as though the animal had been stepping in water. The posterior extremities were stiff-like in movement and spread apart in their gait. Then trembling ensued in the extremities, followed by convulsions of the whole body. In the convulsive state the animal usually made loud cries before and after the convulsion. Conjunctivitis was frequently noted in the tetania parathyreopriva. The sense of hearing, sight, smell, and taste remained. They did not respond to petting. They also had the projecting abdomen noted by Hagenbach.

In some old cats some time after removal

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of parathyroids and thyroids and careful examination of the thymus, no tetany ensued for two weeks. Now, Bell and Martin have shown that pituitary increases the calcium content of the blood. Hence, it is probable that the well-developed pituitary of old animals was sufficient to delay the appearance of tetany, although the animals were kept on a meat diet, which favors tetany. We injected subcutaneously in animals with tetany about ten to twenty grains of pituitary extract, rubbed up with distilled water. Then in about three hours the vacillating, spastic gait disappeared, the tremor was replaced by steadiness, and the lifting of the feet as though wet with water disappeared. The head, which usually hung down, was elevated, and the whole bearing of the animal was changed. This continued for about twenty-four hours, when tetany reappeared. In no case were we able to prevent death by repeated injection of the pituitary. We also injected pituitary by the vein, but the best results were obtained by subcutaneous injections. That neither calcium nor its combination with other salts was concerned in the action of the pituitary was proved by the fact that incineration of the pituitary extract and the injection of the ash was not followed by any curative effect. The extract was subjected to intense heat in a capsule for a couple of hours, then the remaining salts were dissolved in distilled water and injected subcutaneously and by the vein.

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All our observations show that it is an organic body in the pituitary which abates the tetany. We also tried pituitrin, an acidulated extract of the infundibular part of the pituitary. It was used subcutaneously in doses of 4 cc. up to 28 cc. It acts rapidly in the relief of tetany, but the action is much more fugitive than the pituitary extract. Pituitary extract by the jugular is not as effective as subcutaneously.

Adrenalin was given by the jugular, in the cat, and some improvement was noted. Löwenthal and Wiebrecht saw a good effect in human tetany by adrenal extract.

Iodothyrin was also given by the jugular, and it had a quieting action upon the tremor.

Mammary gland, thymus, testicle, prostate, spleen, spinal cord (all rubbed up with distilled water), and Poehl's spermin had no effect upon tetany; they were all given subcutaneously. Pancreas had a quieting effect in seven cases out of ten.

As to the comparative value of pituitary extract and calcium lactate, our experiments did not show any particular difference. The intravenous injection of calcium lactate passed off quickly, while the subcutaneous effect of pituitary came on slower and continued longer.

Pituitrin did not have the permanent effect that the gland substance did. Evidently in tetany the gland itself should be used, as there is something wanting in the pituitrin. The "Vaporole" Extract of Infundibulum (1 cc.)

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20% (Burroughs Wellcome & Co.) may be the best to use. It is inferable that the infundibular lobe is the active part of the gland in antagonizing the tetany after the removal of the parathyroids.

As to the cause of tetany, we have two theories, one of hypocalcification, held by Silvestri, Netter, Quest and MacCallum; the other, that the removal of the parathyroids leaves a poison in the blood (Pfeiffer and Mayer), or, according to Berkeley and Beebe, it is a poison generated in proteid metabolism.

Beebe's experiments showing that strontium will relieve tetany quite as well as calcium indicate that hypo-calcification is not the whole cause of tetany, but only an epiphenomenon.

Our experiments show that:

(1) Removal of the parathyroids alone causes tetany.

(2) Pituitary extract will temporarily cure tetany.

(3) Between the parathyroids and the pituitary there is a co-operative action.

(4) The infundibular lobe contains the active principle.

(5) Tetany is not due to want of calcium, but to a poison in the blood.

The nucleoproteid[1] (S. P. Beebe's method)[2] was used in part of the experiments upon the intestine, uterus and kidney. The gland itself

[1] Thanks to kindness of Dr. W. N. Berkeley, of New York.

[2] *The Old Dominion Journal of Medicine and Surgery*, April, 1909, p. 231.

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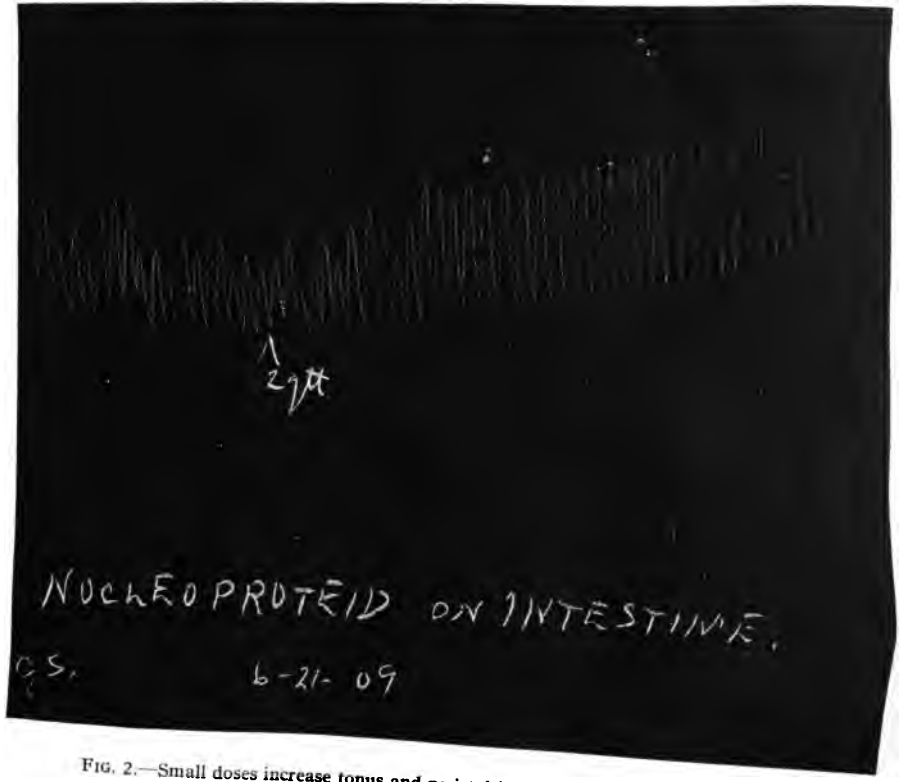

FIG. 2.—Small doses increase tonus and peristalsis—large doses decrease peristalsis.

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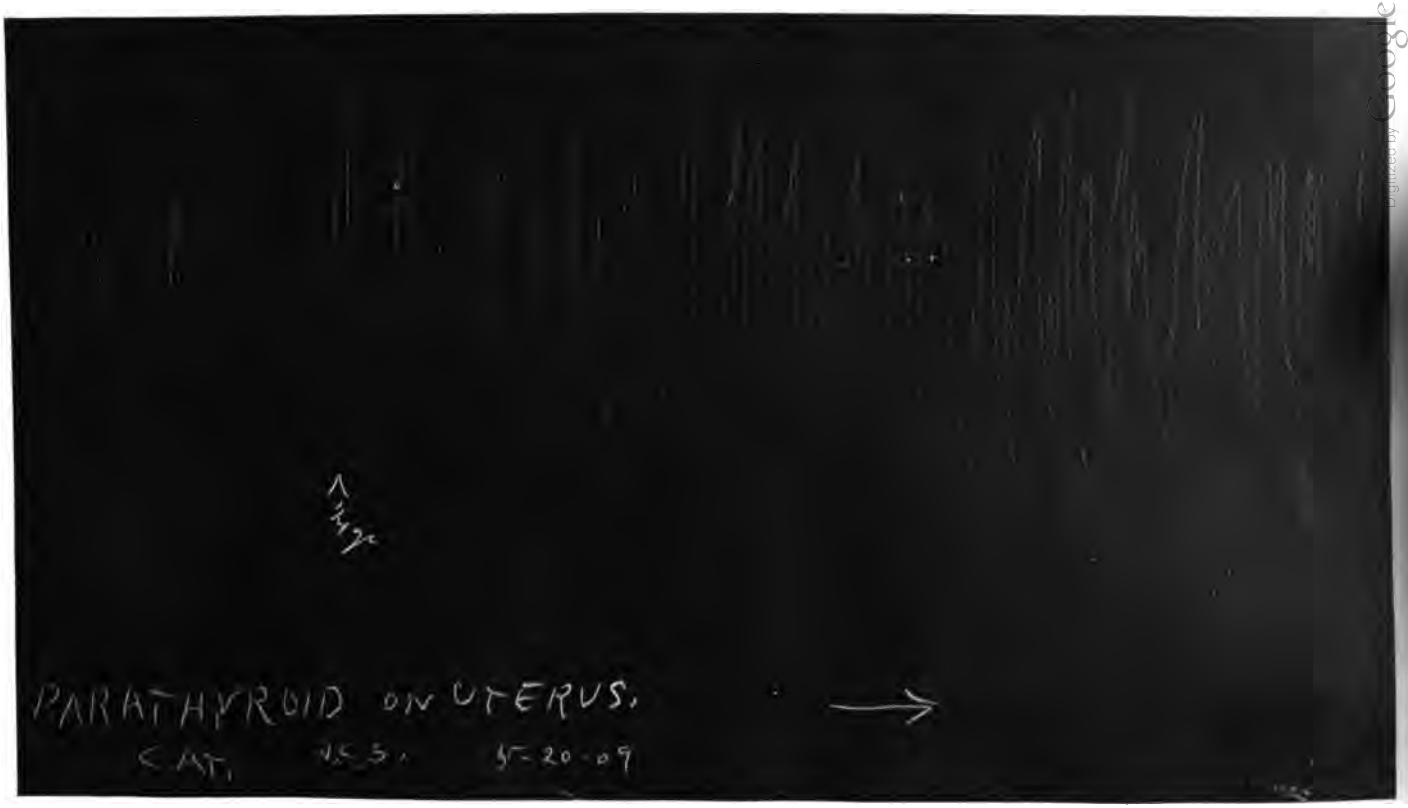

FIG. 3.—Nucleoproteid increases the force of uterine contractions.

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FIG. 3.—Nucleoproteid increases the force of uterine contractions.

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sent drops of urine noted with an

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was also used. It was rubbed up with distilled water, heated and filtered. The intestine and uterine tissue were excised and placed in Ringer's solution and attached to a Porter heart-lever. The oxygen was bubbling through the solution at about the rate of 200 per minute. The temperature of the Ringer solution was 37°·C. It is the method of Magnus. The nucleoproteid increased the tonus and extent of the contractions of the intestine (Fig. 2). It also increased the force of the contractions of the uterine tissue (Fig. 3).

Studies were also made upon the circulation. The arterial pressure after injection per jugular of three drops of nucleoproteid rose slightly and then fell. Doses of ten to fifteen drops caused an immediate fall of pressure. The pulse rate was not changed much (Fig. 4).

In the cat $^1/_8$ grain of the powdered parathyroid per jugular in a watery solution momentarily depressed the pulse rate and later increased it above normal. The blood pressure at the time of the injection fell greatly, but afterwards rose again but seldom to normal.

Respiration.—One-eighth grain of the parathyroid per jugular decreased the rate of respiration. The nucleoproteid by the jugular increased it.

Temperature.—Large doses of the nucleoproteid reduced the temperature in rabbits which were permitted to run about the laboratory.

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Diuresis.—Our experiments were made mainly upon cats; a few rabbits were also used. The animal was bound down, given 5 cc. of paraldehyde by the mouth, then chloroform was given. The abdomen was opened in the median line over the bladder, the bladder drawn out and an incision made into it. A funnel-shaped glass tube with a flange was inserted into the bladder and walls of this viscus tied about the flange. Then the bladder was filled with the urine previously obtained from the bladder. If this was not sufficient to fill the bladder, then Ringer's solution was added. By means of a piece of rubber tubing attached to the funnel-shaped tube the urine was permitted to drop into the capsule. This was done for about fifteen minutes, when each drop of urine was noted on the smoked drum with an electric marker. Then the extract or powdered gland was rubbed up with distilled water, filtered and injected into the jugular. The drops of urine were again noted. The bladder was kept moist with absorbent cotton wet with Ringer's solution. The blood pressure was frequently noted at the time the urine was dropping.

We found that the parathyroid nucleoproteid in some cases increased diuresis in a half-hour tenfold (Fig. 5). The pancreas, thymus and extract of the renal cortex were also found by us to be excitants of diuresis.

This diuretic action by the parathyroids

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ue. Normally it was 4 drops in

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is greater than that of any of the glandular extracts, not excepting pituitrin. It is a direct action upon the glandular epithelium, as it occurs in experiments where the blood-pressure is falling from the beginning.

The small size of the four parathyroids in the cat must secrete a very minute quantity of material to act upon the kidneys. According to the size of the dose, it is probably one of the strongest of all diuretics. Hence the parathyroids, in addition to the maintenance of the reflex activity of the nerve cells, also have another great and important function, the stimulation of the renal epithelium.

Action on Pupil.—Meltzer[1] was first in showing that adrenalin dilated the pupil when locally applied to the eye of a rabbit in which extirpation of the superior cervical ganglion had been done twenty-four hours previously. It had no effect on the normal eye, but Schultz has since shown that large doses frequently applied dilate it also. Our experiments were made upon rabbits. The superior cervical ganglion was excised under ether and next day the nucleoproteid of the parathyroids dropped into both eyes. The intensity of the light was regulated so as to be about the same. The rabbit was placed upon a table and permitted to run over it. The diameter of the pupil was measured with a pair of compasses. On the normal eye it dilated the pupil; on the eye on the side

[1] *Am. Journal of Physiology*, Vol. XI, 1904, p. 28.

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where the superior cervical ganglion was excised it at first contracted and then dilated the pupil.

PATHOLOGY.

Paralysis Agitans.—Dr. W. N. Berkeley, of New York, has put forth a theory, also independently propounded by Lundborg, that this disease can be greatly benefited by the use of the parathyroids. The trembling, rigidity, salivation and the propulsive movements of animals resemble somewhat the symptoms of paralysis agitans. Besides, cases of myxedema and exophthalmic goitre are sometimes associated with paralysis agitans. Here the parathyroids may be involved. On *post mortem* Berkeley has found a sclerosis of the parathyroids. Dr. Camp reported two cases of paralysis agitans in which the parathyroids were diseased. In one there was some colloid material, and in both there was a peculiar infiltration with fat, especially in relation to the blood vessels. Dr. Berkeley, from an experience covering several years, has arrived at the conclusion that nearly all the patients with paralysis agitans slowly respond to the treatment by parathyroids. In 25 per cent. of the cases the response is temporary and imperfect. Seventy-five per cent. showed progressive benefit during the entire period: the rigidity diminished, the pain lessened, salivation was cured, the shaking diminished or was cured, voluntary control of the muscles greatly increased, and restlessness and

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insomnia were nearly or quite abolished. Berkeley states that these glands are antispasmodic in their action, and may be of service in a number of different diseases.

Erdheim, in 1883, found in a case of paralysis agitans a hyperplasia; the oxyphile cells of the parathyroids were unusually enlarged.

Roussy and Jean Clunet[1] in four cases of paralysis agitans found histological evidence of a hyper-function in the parathyroid glands.

MEDICAL TETANY.

Tetany of Gastric Origin.—In two cases of tetany due to dilation of the stomach, and one by an enteritis, there were no corresponding changes in the parathyroid sufficient to account for the tetany. There was a possible insufficiency of secretion by the glandules.

MacCallum (1905) examined the parathyroids in an old man dead from gastric tetany, caused by pyloric stenosis and gastric ulcer. He found five rather large parathyroids, which showed large groups of eosinophile cells undergoing mitosis to a large degree. He inferred a hyperplasia of the glandules. He thinks the dilated stomach generated a poison which the parathyroid secretion neutralized. But as it was an insufficient neutralizer, tetany ensued on account of the excess of the poison.

Berkeley reports a case occurring in the practice of Dr. W. B. James of gastric tetany in a

[1] *Comptes Rendus de la Société de Biologie*, Vol. LXVIII, p. 320, 1910.

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man 35 years old who had extreme dilatation of the stomach. He had violent symptoms, and his life was despaired of. Capsules of parathyroid improved and cured him. Dr. Kinnicutt had a patient with gastric tetany in which the capsules cured the tetany, but the patient died. He had extreme dilatation of the stomach. Calcium lactate given by Dr. Beebe also reduced this patient's tetany.

Tetany of Pregnancy.—Idiopathic tetany was first described in 1830, by Stringheim. N. Weiss, in 1880, connected tetany with thyroidectomy. It has been found that in animals which have two of the parathyroids removed, not all of them, that at the end of pregnancy tetany ensues. After the delivery the tetany disappears. At the end of a second pregnancy tetany again ensues. Here we have a hypoparathyroidism. These facts led to the theory that puerperal eclampsia is due to deficiency of secretion by the parathyroid.

Pepere (1905) had four cases of eclampsia, in three he found two parathyroids missing, and in one he discovered a severe injury of one parathyroid because of a cystic degeneration, while the other three were intact.

Zanfrognini (1905) found in a case of eclampsia only two parathyroids present, and no trace of hypertrophy in them. He also (1905) treated five cases of eclampsia with the parathyroidine of Vassale, when the convulsions ceased, albumen

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disappeared from the urine and the pulse was better.

The tetany can ensue in the first pregnancy, and also take place in the second pregnancy, or it can first occur in later pregnancies. It may take place in the first month, or about the sixth month, or shortly *ante partum*. Its course is inconstant. Weiss saw in the fourth month of pregnancy after a total thyroidectomy a tetany which towards the end of pregnancy stopped, but *post partum* again returned. Meinert (1889) had a case in the fourth month of pregnancy with a one-sided thyroidectomy, and tetany ensued. The second pregnancy was free from tetany. In the eleventh pregnancy strong tetany ensued about the eighth month. Several cases are recorded similar to the above by Von Eiselsberg, Westphal, Peham, and Dienst.

Tetany of Infants.—In two cases of tetany of infants, Erdheim found in both cases a hemorrhage in the parathyroids.

Haberfeld has found that the parathyroids can be a seat of hemorrhage causing a hypoplasia. It is in the parenchyma of the gland that the lesion is seated. He found in many cases of tetany in children that the parathyroids were the seat of hemorrhage.[1]

SURGICAL TETANY.

Tetany Due to Surgical Procedures in Man.—In 1886 Billroth did a total thyroidectomy

[1] *Wiener Klin. Wochenschrift*, XXIII, 27, p. 1017.

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for an adenocarcinoma of the thyroid, and a temporary tetany ensued. In 1892 a second operation was made on this patient, a resection of the manubrium sterni. On the ninth day after the operation tetany ensued and recurred often in the following years. It is supposed that the first operation removed only part of the parathyroids, while the second operation injured the glandules in the thymus, as there was metastasis in the neck at the time of the second operation. Kocher observed a tetany resulting in death after ligature of four of the arteries supplying the thyroid, and Kopp also observed tetany after ligature of two and three arteries of the thyroid. Dr. J. J. Putnam, of Boston, in a case of post-operative tetany, greatly relieved the tetany by the use of the parathyroid capsules of Berkeley.

Halstead (1907), of Baltimore, Pool (1907), of New York, and Branham (1908), of Texas have reported cases of tetany after thyroidectomy. Halstead's case was greatly relieved by parathyroids.

In case of carcinoma of the thyroid the whole gland must be removed, notwithstanding the tetany, as it can be alleviated by the means already specified. The great number of operations now for exophthalmic goitre and goitre proper make surgical tetany an important subject. Patients with Graves' disease bear badly the loss of parathyroids.

In disease of the thyroid not malignant the

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surgeon must not only leave a part of the thyroid to prevent myxedema, but also the parathyroids to prevent tetany. Two of these bodies in man are extra-capsular and can be avoided in the operation. If all the parathyroids are removed, then transplantation of these bodies must be attempted.

Transplantation of Parathyroids for the Cure of Tetany.—Transplantation does not succeed unless some of the parathyroids have been previously removed.

Von Eiselsberg, in 1892, transplanted the parathyroids successfully, and they were functionally active.

Many others have done the same. W. S. Halstead,[1] of Baltimore, has found that autotransplantation of parathyroid glandules into the thyroid and behind the rectus abdominis muscle has been successful in 61 per cent. of cases in which a deficiency greater than one-half of the parathyroids had been created. Isotransplantation has been uniformly successful. One parathyroid graft may suffice to maintain the animal in good health and spirits for many months.

Danielsen[2] relates a case of tetany occurring on the sixth day after a thyroidectomy. The transplants from two other parathyroids which had been removed and placed between the fascia and the peritoneum cured the tetany.

[1] *Journal of Experimental Med.*, Vol. XI, No. 1, p. 198.
[2] *Munchener Medizinische Wochenschrift*, 1910, p. 973.

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In mild cases of tetany he recommends 3 grains chloral a day, and protracted warm baths.

Messrs. Herman and Harvey[1] have made a series of experiments upon dogs, and have found that auto-transplantations are more successful than iso-transplantations. They think the visceral peritoneum is superior to the spleen as a site for the transplantation of parathyroid. They also show that isotransplantation is possible.

Schneider[2] reports a case of sarcoma of the thyroid and parathyroids whose removal was followed by severe tetany. Fresh parathyroid substance from the horse, dried and powdered, was given and he says that a specific favorable effect on the tetany was unmistakable. The patient was a woman of 40. She succumbed, before the year was out, to the progress of the malignant disease.

Tumors of Parathyroids.—Berard and Alamartine[3] found from an examination of the parathyroids a case of tumor of one parathyroid. From the records they have assembled twenty-nine cases of tumor of the parathyroid. Of these cases three were malignant, and metastasis proved fatal after removal of the primary tumor. In twenty-four cases the tumor was formed solely of parathyroid tissue, while in five there were islands of thyroid tissue. Rapid growth

[1] *University of Penna. Medical Bulletin*, June, 1909, p. 136.
[2] *Journal of Am. Med. Association*, 1910, p. 1912.
[3] *Journal Am. Med. Association*, 1909, p. 241.

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of a tumor in a parathyroid indicates malignancy.

Changes in Teeth.—Erdheim noted not only tetany in the rat, but changes in the teeth with which the rat gnaws. The enamel on the anterior surface of the teeth becomes opaque, and white spots appear in it. The teeth often break off in the alveolus. This happens first in the upper jaw, then in the lower. The microscopic changes in the teeth show changes first in the dentine, then in the enamel and its epithelium. There is a hypocalcification in the dentine. After the fracture of the teeth, the teeth in the antagonizing jaw attain great length. Erdheim has also noted changes in the lens, resulting in cataract. In four cases of puerperal eclampsia, there was hyperemia of the parathyroids and in two one of the parathyroids had a small circumscribed spot, an injury of the parenchyma, and in one of these two cases a small hemorrhage into the glands.

Erdheim believes that there is a connection between osteomalacia and parathyroid insufficiency, the direct result of the involvement of calcium metabolism.

Osteomalacia puerperalis, according to Erdheim, is associated with disease of the epithelial bodies. Here he found often hypertrophy of the parathyroids and consequently a hyperparathyroidism.

In congenital cretins, where the thyroid is absent, the symptoms of cretinism continue

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although all the parathyroids are present. The growth of the bones in these cases is retarded; the presence of the epithelial bodies does not prevent it. They are not converted into thyroid tissue, as held by some English physiologists.

Roussy and Clunet[1] have studied the thyro-parathyroid apparatus in two congenital cases of myxedema aged 28 years. They found the thyroid reduced to the volume of a grain of wheat and it had an embryonic histological structure comparable to that met with in the first months of fetal life. The parathyroids were well developed, the volume of each one exceeded by 30 to 40 times that of the thyroid; their structure was normal without any sign of hyper- or hypo-function. These adults confirm the generally admitted fact of the embryological, anatomical and functional independence of the parathyroids and the thyroid;

Hair.—Pfeiffer and Mayer noted a great shedding of hair in rats during tetany.

Paraesthesia.—Vassale noted, in a bitch after he had removed the three parathyroids during the period of lactation, a pruritus of the nose. Erdheim pointed out that after tetany in rats, due to removal of the parathyroids, they spent a great part of the day in making a toilet for their nose. They even used, in addition to their anterior extremities, their posterior extremities to scratch their nose, and did it con-

[1] *Compt. rend. Société de Biologie*, 1910, p. 818.

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tinuously and in a cramp-like manner until they were tired. Then after a rest they continued the scratching. Erdheim has also noted in tetany of pregnant women a paraesthesia.

Vincent and Jolly and Berkeley have alluded to the curious "paw shaking" on the second day after removal of the parathyroids. We have also noted this action in the cat, as though the cat had wet his foot by stepping in water. It is a paraesthesia, and probably due to changes in the center of touch.

Uterine Inertia.—In pregnant women who have tetania parathyreopriva, abortion has ensued; there was atony of the uterus and tamponing had to be resorted to. I have shown that the parathyroid extract strongly excites uterine contraction, and its absence may account for the uterine atony. The parathyroids have close relations with the sexual organs.

Urinary Secretion in Nephritis.—In a case of chronic interstitial nephritis, one grain of the gland three times a day by the mouth increased the quantity of urine a half pint daily in forty-eight hours. In this case, a man of 65 years of age, it seemed to produce an extremely frequent desire to micturate.

Glucose.—After the injection of nucleoproteid of the parathyroid by the vein, glucose appeared in the urine to the extent of $1^1/_2$ per cent., as shown by the fermentation test and Fehling's test.

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IT MAY BE CONCLUDED:

(1) That the parathyroids are embryologically, histologically and physiologically distinct from the thyroids. The only thing they have in common is their position in the neck.

(2) The parathyroids, unlike the thyroids, contain no iodine.

(3) Deficiency of the secretion by the parathyroids is the cause of tetany.

(4) The tetany from removal of the parathyroids can be greatly benefited by pituitary extract, calcium, strontium and parathyroid extract. They can carry the patient along until the small piece of parathyroid can hypertrophy and supply the secretion.

(5) The grafting of a parathyroid is a cure for tetany.

(6) When the parathyroids cause tetany, they do it by absence of their secretion, and not by calcium changes.

(7) In tetany there is a poison in the blood which has been found to kill mice when the serum is injected.

(8) That hypocalcification is affirmed and denied by experimental tests to exist in tetany. The calcium changes are only an epiphenomenon.

(9) Of all the glandular extracts the parathyroids are the most powerful diuretics. They act directly on the renal epithelium, as the urinary secretion is increased when the arterial

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tension is lowered from the beginning of the injection of nucleoproteid by the jugular.

(10) The parathyroids increase uterine contractions and intestinal peristalsis.

(11) When locally applied, the nucleoproteid of the parathyroid dilated the pupil.

(12) The nucleoproteid of the parathyroid in small doses momentarily increases and then decreases the arterial tension. Large doses decrease it at once. The pulse is decreased by powdered parathyroid and then increased.

(13) Nucleoproteid increases the rate of respiration. Powdered parathyroid decreased it.

(14) Large doses of the nucleoproteid lowers the temperature.

I cannot close with better words than those uttered to the students of this college in 1896, in an introductory lecture by me. They are as true now as they were thirteen years ago.

Glandular physiology, in its wide-spread ramifications, applied to other ductless glands of the body, has revolutionized many parts of physiology and pathology. It is only in its infancy. Its maze of metabolic changes hold many facts to be discovered. The secretion of the ductless gland opens up new avenues of investigation, which will enrich the science of physiology and the practical application of these facts in therapeutics. We have a silent and hitherto unsuspected secretion going on which plays a most important and unknown part in our economy.

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Very potent remedies are the ductless glands, where but a few millionths of a grain of a gland, like the adrenal, greatly elevated arterial tension. Several of these animal extracts, as I have shown, are thermogenic agents; others are not. Some, like the thyroid, greatly depress the rate of the heart.

When we see the cures produced by the thyroid powder, in myxedema, cretinism, and obesity, when we see the changes of acromegaly arrested by the pituitary, Addison's disease improved by the adrenals, we can not help noting their power. We see in the action of these extracts the simple external manifestations of the great forces at play in the nutrition of the economy.

REFERENCES:

QUEST: *Wiener Klinische Wochenschrift*, 1906.

NETTER: *Comptes Rendus de la Société de Biologie*, 1907, page 376.

HAGENBACH: *Mitteilungen aus den Greanzgebieten der Medizin und Chirurgie*, 1907, p. 330.

ERDHEIM: *Mitteilungen aus den Grenzgebieten der Medizin and Chirurgie*, Band 16, Heft 4 × 5, p. 632.

PFEIFFER UND MAYER: *Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie*, 1907, p. 379.

MACCALLUM: The Physiology and Pathology of the Parathyroid Glands. *Proceedings of the Pathological Society of Philadelphia*, 1908, April and May.

BEEBE: The Inhibition of Tetany by Extract of the Parathyroid. *Am. Journal of Physiology*, Vol. XIX.

W. G. MACCALLUM AND VOEGTLIN: *Journal of Experimental Medicine*, Jan., 1906.

BERKELEY AND BEEBE: *Journal of Medical Research*, Feb., 1909.

Digitized by Google

BELL AND HICK: *British Medical Journal*, 1909, p. 517.

PEPERE: *Le Ghiandole Paratiroidee*, 1906.

VINCENT AND JOLLY: *Journal of Physiology*, Vol. XXXII, p. 65.

W. S. CARTER: *Texas State Journal of Medicine*, Jan., 1908.

MOUSSU: *Recherches sur les Fonctions Thyroidienne et Parathyroidienne*, 1897.

MINKIEWITSCH: *Tetania parathyreopriva und Hyperparathyreosis*, 1908.

FORSYTH, DAVID: *The Quarterly Journal of Medicine*, 1908, Vol. I, Nos. 2 and 3.

GEISS: *Ueber tetanie nach partial strumectomie*-Inaugural Dissertation Göttingen, 1902.

A. BIEDL: *Innere Secretion*, 1904.

A. FROUIN: *La Presse Medicale*, 1909, No. 62, p. 609.

L. COTONI: *Revue de Medicine*, 1909, No. 8, p. 615.

KARL PETREN: *Upsala Läkareförenings Förhandlingar*, 1909–'10, Häft 102, p. 1.

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SECOND LECTURE—THE PITUITARY.[1]

Gentlemen:—Last year the parathyroids served as a subject for the introductory lecture. As the ductless glands have been the object of much experimentation in conjunction with Dr. J. C. Scott in our laboratory, I have selected this year the pituitary gland, which is fast coming into great prominence both in surgical and in therapeutical relations. In the lecture I shall use the words hypophysis and pituitary as interchangeable in meaning. For excess of secretion, hyperhypophysy; for deficit of secretion, hypohypophysy. I prefer these words to hyperpituitarism and hypopituitarism.

I shall not consider the surgical procedures for the removal of the gland. In this lecture only the main points will be taken up, but they will bear on the practical side of medicine.

The hypophysis is situated at the base of the brain in the sella turcica of the sphenoid bone (Fig. 6). In man the pituitary weighs about ½ gram.

Diameters of Pituitary Fossa.—Porier makes the diameters of the pituitary fossa as follows:[2]

Male (anterior-posterior.)	Female.
0.75 to 1.45 centimeters	0.75 to 1.30 centimeters
Transverse	
0.70 to 1.50 centimeters	0.80 to 1.50 centimeters
Depth	
0.60 to 1.20 centimeters	0.60 to 1.39 centimeters

[1] Lecture delivered Sept. 28, 1910, before the Sophomore Class of the Medico-Chirurgical College of Philadelphia.

[2] Jaugeas, *Les Rayons de Röntgen dans le diagnostic et traitment des Tumeurs Hypophysaires*, 1909.

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Chemical Nature.—Simpson and Hunter found in eleven fresh pituitaries of the slaughter-house from the sheep a minimal amount of iodine—

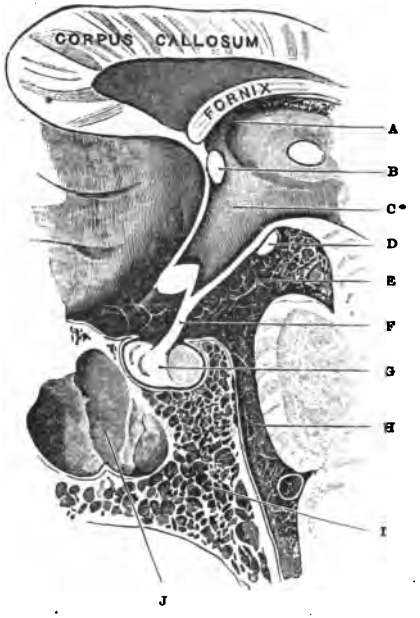

FIG. 6.—Mesial section through the pituitary region in the child.

A. Foramen of Monro.
B. Anterior Commissure.
C. Ventricle III.
D. Corpus mammillare.
E. Subarachnoid tissue in cisterna basalis.
F. Infundibulum.
G. Pituitary body.
H. Cisterna pontis.
I. Basi-occipital.
J. Sphenoidal sinus.

not more than 0.005 milligram. In sheep they removed the thyroid, leaving behind the

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two external parathyroids, and after forty-seven to fifty-six days the sheep were killed, but no iodine was found in their pituitaries.[1] Halliburton, Candler and Sikes[2] found no iodine in the human pituitary by Baumann's method.

Dr. H. Gideon Wells[3] analyzed twenty-two pituitaries from patients who had not received iodine while in the hospital. He did not find a trace of iodine by Baumann's method. In three glands from patients who had received iodine he found a trace of iodine, probably about 0.02 milligram. The inference is that the pituitary contains no iodine.

W. Neubert found glycogen constantly in the epithelium of the colloid cysts lying in the boundary between the anterior and posterior lobes. It is also found in the nervous portion of the hypophysis. This glycogen is markedly increased in diabetic cases.[4]

Histology —The pituitary is composed of three parts: (1) the large anterior epithelial lobe, pars anterior; (2) a much smaller posterior, nervous or infundibular lobe, pars posterior; and (3) the pars intermedia. The ectoderm of the mouth (Rathke's pouch) originates the anterior lobe, which soon becomes a glandular structure. An outgrowth from the floor of

[1] *Quarterly Journal of Experimental Physiology*, Vol. III, No. 2, p. 121.

[2] *Quarterly Journal of Experimental Physiology*, 1909, p. 229.

[3] *Journal of Biological Chemistry*, Vol. VII, No. 4, p. 250.

[4] *Beiträge zur Path. Anat. und zur Allg. Path.*, 1909, XIV, 38; *Journal of Am. Medical Association*, No. 24, p. 2023, 1909.

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the third ventricle from the infundibular pouch of the thalmencephalon, the mid-brain, develops the posterior lobe. The posterior lobe consists of two parts: (1) the neuroglia cells and fibers with ependymal cells, and (2) the pars intermedia, composed of epithelial cells from a diverticulum of buccal epithelium, the posterior pharynx, and is ectodermic in origin.

Herring finds in the cat the posterior lobe of the pituitary is hollow and its cavity is in free communication with the third ventricle of the brain, while the epithelium of the anterior lobe affords a nearly complete investment of the posterior lobe. In the dog the posterior lobe is solid, but the neck is hollow and in communication with the third ventricle. The epithelial part of the pituitary is composed of two distinct parts, an anterior lobe consisting of solid columns of cells, and a pars intermedia which lies between the anterior lobe and the nervous tissue, forming a close-fitting investment of the latter. The anterior lobe contains cells which are clear or hold in their protoplasm varying amounts of granules which stain deeply. The pars intermedia consists of finely granular cells, in layers of various thicknesses and closely applied to the posterior lobe. Colloid material is found between the cells of the pars intermedia, which appears to pass into the nervous substance of the gland and then into the third ventricle. The infundibular or nervous part is made up of neuroglia

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cells and fibers. It has no true nerve cells, and the nerves supplying the pituitary probably reach it through the sympathetic fibers supplying the blood vessels. The nervous part contains columns of epithelial cells from the pars intermedia, and islets of these cells are found in the substance of the infundibular lobe. The nervous part contains large amounts of colloid like that of the thyroid.[1]

The anterior lobe is a gland which must discharge its secretion directly into the vascular sinuses. The secretion of the pars intermedia seems to be secreted into the substance of the brain.

The function of the pars intermedia is to generate a colloid material which acts upon the circulation and the kidneys.

Haberfeld has examined the pharynx in man for remains of the embryonal diverticulum which finally forms the pituitary. He investigated fifty-one subjects whose ages ranged from fetal life to old age. In all cases he found a definite structure which he calls the pharyngeal pituitary gland. It is made up of a string of cells, is 5 millimeters in length, and runs immediately behind the vomer upwards and backwards. It is composed of cells similar to those in the pituitary, but the chief cells are the "Hauptzellen."[2]

[1] Herring, *Quarterly Journal of Experimental Physiology*, 1908, Vol. 1, No. 2, p. 156.

[2] *Beiträge zur Path. Anat. u. zur Allgemein Path.*, 1909, p. 133.

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The pars anterior contains three kinds of cells: (1) the "Hauptzellen;" (2) Eosinophiles; (3) Basophiles. Erdheim and Stumme call the eosinophiles or acidophiles and basophiles or amphophiles or cyanophiles because their protoplasm intensely takes up stains, the chromophiles, while the "Hauptzellen" they call chromophobes, because their protoplasm is very difficult to stain. The most numerous cells are the eosinophiles, the next in number the basophiles. The "Hauptzellen" are less in number than the eosinophiles and the basophiles, and usually are found in the center of the alveolus.

The importance of these cells in the secretion of the hypophysis has been the subject of several theories. Thom holds that the strongly staining chromophile cells produce a secretion in the form of fine granules. Their cell walls are indistinct, the nucleus moves towards the periphery, the granules escape and mix with an incolorable secretory material furnished by the chromophobes. Scaffidis, like Thom, makes two kinds of secretory cells, so that the glandular secretion is a mixture of two processes of secretion. In the secretion of the two types of cells, one reacts to an acid, the other reacts to an alkali; these both concur to form the colloid secretion of the hypophysis. Launois holds a view similar to that of Scaffidis.[1]

The majority of authors believe the colloid

[1] *Launois, Thèse*, Paris, 1904.

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is the normal secretion of the hypophysis. Cagnetto in a case of acromegaly found the chromophile cells and colloid increased, while in a case of tumor of the hypophysis without acromegaly both chromophile cells and colloid were diminished. A few authors believe they have seen the passage of the colloid into the blood.

Comte[1] in 1898 noted an increase in the size of the pituitary in pregnancy. Erdheim and Stumme[2] have examined twenty-five normal pituitaries. They make three types of cells.

During pregnancy the hypophysis increases in weight and size and this increase is in the pars anterior, the pars posterior remaining unaltered. At the end of pregnancy the "Hauptzellen" are increased so much in number that the eosinophiles, unchanged in number, take the second place. A few weeks after delivery the pregnancy cells decrease and at the end of the second year post-partum the eosinophiles are again predominant. The number of basophiles remains the same in pregnancy. The "Hauptzellen" are the cells in which the peculiar changes caused by pregnancy take place, as they are enormously increased and considerably hypertrophied. These pregnancy cells in time atrophy and become the "Hauptzellen." The number of "pregnancy cells" by multi-

[1] Comte, *Contribution a l'Etude de l'hypophyse*, 1898.

[2] *Beiträge zur Path. Anat. und zur Allgemeinen Path.*, p. 1, 1909.

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para is undoubtedly much greater than in the primipara.

They claim that a skilled histologist can diagnose a former pregnancy from the pituitary gland. The swelling of the gland is quite definite and in two cases there was a hernia of the gland through a hole in the dura which accommodates the infundibulum.

The bloated face, the swollen lips and the enlargement of the hands have been referred by Tandler and Gross to the enlargement of the hypophysis by pregnancy—a hypersecretion.

These facts have been used as an argument to support the theory of hypersecretion in acromegaly. Von Reuss observed a bitemporal hemianopsia in the course of a 14″, 15″ and 16″ pregnancy, which gradually disappeared after delivery. He thought there was a large pituitary pressing upon the optic chiasm which caused the hemianopsia.

Coagulation of Blood.—Weil and Boye and Levan have shown in rabbits, dogs and man that intravenously the posterior lobe causes coagulation with great rapidity, notwithstanding the alkaline solution in the manometer tube. After an injection by the vein of the anterior part of the pituitary, coagulation is the exception. If the whole pituitary is injected then coagulation[1] is also exceptional.

Herry[2] found that the extract of fresh organs

[1] *Compt. rendus de la Soc. de Biologie*, p. 618, 1909.
[2] *Compt. rendus de la Soc. de Biologie*, p. 603, 1910.

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(as spleen, kidney, lung, liver, thymus and hypophysis) more completely corrected the difficulty of coagulation of the blood in hemophilia than fresh serum. Extracts from the dried organs did not coagulate blood as well as the fresh organs.

Action of Pituitary on the Circulation.—Oliver and Shaefer (1895) stated that aqueous or saline extracts may be boiled without losing their activity and when injected produced a rise of blood pressure. They also showed that it was due to an action on the arterioles. Howell (1898) found that it was the infundibular lobe which elevated blood pressure. He also noted a slowing of the heart. Shaefer and Swale Vincent (1899) found the cardiac slowing observed was not constant and that slowing ensues after section of vagi or previous atropinization. Hence, the seat of the slowing is peripheral. Adrenalin acts on the vagus center. Shaefer found that the second or third dose did not produce a rise but invariably a fall which lasts but a short time.

Shaefer and Swale Vincent believe this to be due to a depressor substance, and that this substance is soluble in alcohol, in which the pressor substance is insoluble. This depressor substance is not identical with choline as the previous use of atropin does not prevent the fall as is the case with choline.

Circulation, Effect of Anterior Lobe.—Dr. W. J. Hamburger found, as previous observers

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did, that the intravenous injection of a saline extract of the anterior lobe caused a distinct fall of blood-pressure. This was usually accompanied by an acceleration and weakening of the heart. That a second injection immediately following the first does not produce any change in blood pressure. After a considerable interval the second injection produces a fall. In a number of dogs the fall of arterial tension was succeeded by an apparent toxic action resulting in death. The depressor substance is soluble in alcohol, glycerin and salt solutions, but insoluble in ether.

A secondary rise above normal follows the depressor effect produced by an alcoholic extract of the anterior lobe.[1]

Fodera and Pittau[2] studied the hypophysis. They did not confirm Von Cyon's statement that the greatest activity was in boiled extracts, being superior to those obtained in the cold or at a temperature below that of ebullition, or that the extracts of dried glands were better than those obtained from fresh glands. They could not find the slightest difference in their activity. They experimented upon frogs and rabbits. Between the extracts of the posterior lobe as a whole and those of the posterior lobe deprived of the small epithelial layer there was no qualitative difference but

[1] *American Journal of Physiology*, Vol. XXVI, p. 178.
[2] *Archives Italienne de Biologie*, Tome LII, Fasc. III, p. 370, 1909.

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only a slight quantitative difference in favor of the true posterior lobe.

In regard to the question of Salvioli and Carraro, about the importance of the epithelial layer in the production of the phenomena of posterior lobe, they answer in the affirmative. They believe that the epithelial layer secretes a substance which penetrates into the infundibular lobe and may be still further elaborated. The anterior lobe is completely inactive, as the activity of the whole lobe is no more active than the posterior lobe alone. They obtained no effect upon the heart and blood vessels of the frog by pituitary extracts. In dogs they confirm Salvioli and Carraro that the extracts of the hypophysis cause a short characteristic diarrhea followed by tenesmus. Intravenous injections are active. Hypodermic injections and use by the mouth, even intracerebral injections are inefficacious. Extracts of the hypophysis of the cow, when given in large doses to dogs and repeated many times a day, cause emaciation. They did not find any prophylactic or anaphylactic properties by intravenous injections in dogs.

The Active Principle.—Is there more than one active principle in pituitary? Malcolm obtained different results in metabolism between the fresh and dried gland. Shaefer has obtained diuretic results without blood pressure action. Dale has thrown considerable doubt upon the theory of more than one active prin-

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ciple. We have found pituitary extracts that did not elevate blood-pressure but did have diuretic effects.

Does the hypophysis contain adrenalin? Both raise blood pressure, both dilate the pupil of the enucleated frog's eye, both subcutaneously produce glycosuria in rabbits. Adrenalin frequently injected produces sclerosis of the aorta. Meyers[1] has shown that pituitary extract can also injure the blood vessel. W. W. Harvey has produced sclerotic effects in the coronary arteries by repeated injections of the hypophysis.[2]

Borchardt[3] noted the absence of adrenalin in the hypophysis, since Vulpian's test, the addition of iron chloride, produced no green color, as adrenalin does. There are two reactions for adrenalin, which are very sensitive and characteristic. The first is that of Comessati. It is a red color by the oxidation of adrenalin. Comessati used a 2% sublimate solution as an oxygen bearer; but Frankel and Allers[4] have shown that the reaction ensues with other oxidizing substances, as copper sulphate, potassium chlorate, and platinum chloride. Frankel and Allers,[4] have proposed a new test for adrenalin. Adrenalin gives, with a slight blue shade, a red color in the presence of some phosphoric acid, heated with a

[1] *Zeitschrift für physiological Chem.*, 1903.
[2] *Bio-Chemical Journal*, p. 431, Vol. IV, No. 9.
[3] *Zeitschrift für Klin. Med.*, Bd. 66.
[4] *Münchener Med. Wochenschrift*, p. 1478, 1909.

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N/1000 biniodate of sodium solution. A dilution 1:300,000 shows a perceptible reaction. This test and that of Comessati with pituitrin of Parke, Davis & Co. showed a negative reaction.

Hence adrenalin and the active principle of the pituitary are not the same substance.

Action on Kidneys.—Schäfer and Herring[1] have shown that the infundibular part of the pituitary body yields a substance soluble in water and not destroyed by boiling, which has a specific action on the kidney, dilating the renal vessels and increasing the secretion from the tubules. If the urinary flow is suppressed from operative procedures or the anesthetic, it causes a flow. They think it is as actively diuretic as caffeine citrate. They found when there was a general fall of blood pressure with no increase, but even a shrinkage of the volume of the kidney, a diuretic action, indicating a stimulation of the renal epithelium. This shrinkage of the kidney precedes the dilatation in some cases. Pituitary was found to diminish the flow of pancreatic juice.

Hypodermically, the pituitary also. slightly raises blood pressure, dilates the kidney vessels and increases the rate of flow of urine. They also point out that the adrenals and pituitary each consist of two parts, one epithelium, the other part of neuroectodermic origin. The

[1] *Philosophical Transactions of the Royal Society of London*, pp. 1–29.

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epithelial parts of these two glands do not yield any physiological effect, while those of neuroectodermic origin furnish substances affecting the heart and arteries. Here the similarity ends, for adrenalin excites the sympathetic terminals in general, while the pituitary does not.

Houghton and Merril[1] have studied the action of adrenalin and the active principle of the pituitary gland upon the urinary secretion. Pituitary slowed the pulse rate after the use of atropin and after section of vagi. Aldrich obtained a crystalline picrate and a sulphate from the infundibular part of the pituitary. They found adrenalin to increase the blood pressure and the flow of urine. They experimented on normal man for several days where the food, drink, habits, exercise and work were the same. Then pituitary extract was given internally. They found only a slight increase of the urine in man.

Then they made experiments upon dogs, anesthetized by morphine and chloretone with cannulae in the ureters. The drops of urine were recorded with the blood pressure and the respiratory movements. Adrenalin increased the blood pressure from 56 to 88 mm. of mercury which within six minutes had returned to normal. The urine increased from 8 minims per minute to 30 per minute, the maximum following closely the maximum blood pressure. The increase of urinary flow continued after the fall

[1] *Journal Am. Medical Association*, 1908, p. 1849.

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of blood pressure to normal, and at the end of fifteen minutes it was the same as at the beginning of the experiment. They also perfused excised kidneys, noting the flow from the renal vein and ureter, and found that pituitary extract added to saline solution made the venous flow and ureteral flow less than when saline alone was used. They do not believe in a specific action on the kidney cell, and if so it is less marked than in the case of a 1 per cent. saline solution. It is due to a rise in blood pressure.

Pal noted in cats that the diuretic effect of pituitary extract was marked, when given intravenously. He emptied the bladder of a cat to which morphia and curare had been given, and found that the intravenous injection of two cubic centimeters of pituitary extract filled the bladder in a very short time. As is well known, the bladder is generally empty after curare narcosis. Pal's experiments as to the size of the kidney after the use of pituitary were not uniform like those of Schäfer. Pal found that pituitary dilated the renal artery and contracted the coronary arteries.

Pal,[1] like Langendorff, found adrenalin dilated the coronary artery, while contracting the renal and other arteries. He found pituitary extract to dilate the renal arteries, but to contract the coronary and other arteries.

We made 20 experiments. The volume of

[1] *Wiener Medizinische Wochenschrift*, 1909, p. 138.

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the kidney was registered by means of an air oncometer and Albrecht's piston recorder.

Our experiments were mainly made upon cats; a few were made with rabbits. The animal was bound down, given 5 cc. of paraldehyde by the mouth. Then chloroform was given. The abdomen was opened in the median line over the bladder, the bladder drawn out and an incision made into it. A funnel-shaped glass tube with a flange was inserted into the bladder and the bladder tied tightly about the flange. Then the bladder was filled with the urine previously obtained from the bladder. If this was not sufficient to fill the bladder, Ringer's solution was added. By means of a piece of rubber tubing attached to the funnel-shaped glass tube the urine was allowed to drop into the capsule. This was permitted for about fifteen or twenty minutes when each drop was noted on the smoked drum with an electric marker. Then the extract of the gland, rubbed up with distilled water and filtered, was injected into the jugular and the drops of urine again noted on the drum. The bladder was kept moist with absorbent cotton wet with Ringer's solution. The blood pressure was frequently noted at the time the drops of urine were registered.

The infundibular part of the pituitary is a diuretic. As it does not markedly increase the general arterial tension except for a moment and then lowers it, it is inferable that the very

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short rise of blood pressure does not produce diuresis which continues a considerable time after the rise of blood pressure.

As the variations of arterial tension do not play any part in the diuresis, it must be referred to an action of the renal epithelium itself (Fig. 7).

Schaefer states that the anterior part of the pituitary has no diuretic effect. The pars intermedia also increases the secretion of urine.

Glycosuria.—It is one of the most frequent symptoms of acromegaly. Hansemann found it 19 times in 97 cases, while Marie observed it in one-third to one-half of his cases. In all these cases of acromegaly with glycosuria they found hypertrophy, glioma, sarcoma, adenoma and epithelioma of the pituitary. Thaon in a case of beginning neoplasm of the hypophysis found a notable hypertrophy of the islets of Langerhans, but there was no diabetes. Lorand considered that lesions of the thyroid and pancreas played a great part in the production of glycosuria in acromegalic patients.

Caselli destroyed the posterior lobe in a dog without touching the anterior lobe, and glycosuria appeared.[1]

Polyuria and sometimes glycosuria occurs in animals with a partial removal of the anterior and a total removal of the posterior lobe according to Cushing.

Borchardt[2] has proved that the hypodermi

[1] *Presbeanu, Thèse*, 1909, p. 70.

[2] *Zeitschrift für Klinische Medizin*, 1908, Band 66, p. 332.

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use of the pituitary produced a small amount of sugar in the urine. He used the boiled filtered infusion of the gland, which was injected hypodermically in rabbits and dogs. The quantity of sugar obtained by him varied from a trace to 4.2 per cent. The absolute quantity of sugar was very small, not more than a centigram. The sugar usually began to appear in the urine three hours after the injection. The amount of sugar excreted was extraordinarily variable and to a great degree independent of the amount of the gland injected. He found that pituitary produced glycosuria more easily in rabbits than in dogs.

Infundibulin.—We have also studied the effect of injections of infundibulin in rabbits and cats. The number of our experiments was fifteen. The tests for glucose were Fehling's, fermentation and the phenylhydrazine tests. The injection of these extracts of the glands proceeds on the theory that they act like a hypersecretion of the gland. The first extract used was infundibulin 20 per cent. extract of the pituitary (Burroughs Wellcome, & Co.). Borchardt used the whole gland to produce sugar. Falta was unable to obtain in rabbits any glycosuria with pituitrin, which is obtained from the infundibular part of the pituitary.

We have made several experiments with infundibulin, of which we injected 1 cc. into the muscles of the rabbit, as Meltzer has shown that adrenalin is more rapidly absorbed here

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than under the skin. In all cases at the end of two and a half hours we found glucose in the urine, the amount being about one-eighth per cent.

In cats intramuscular and intraperitoneal injection of the infundibulin produced similar results. In acromegaly Hinsdale found in an analysis of 130 cases that 10.8 per cent. had sugar. Borchardt from an analysis of 176 cases of acromegaly holds that glycosuria is more regularly associated with this disease than with any other. However, there are cases of tumor of the hypophysis without acromegaly and which are not complicated with diabetes. Kollaritz has collected 51 cases of this nature. From our experiments we must infer that the glycosuria is due to a hypersecretion of the infundibular part of the hypophysis, perhaps of the pars intermedia.

Seat of the Glycosuria: (1) *Removal of Thyroid.*—In etherized cats we extirpated the thyroid, leaving two or more parathyroids. On the following day we found sugar in the urine in a few cases. A similar result after removal of the thyroid has been found in dogs by Falkenberg and Rahel Hirsch.[1] Falta, however, did not obtain it in dogs. We found, however, that the injections per jugular of the same dose of infundibulin in the cat after the absence of the thyroid was followed by a decrease in the amount of sugar as compared with those animals

[1] *Zeitschrift für Klinische Medicin*, 1908, p. 6.

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whose thyroid was intact. Before the removal of the thyroid, infundibulin caused 3 to 4 per cent. of sugar in the urine; after the removal, 1 to 2 per cent. We took care that the binding down and the etherization did not produce glycosuria.

(2) *Removal of Adrenals.*—In the etherized cat we removed the adrenals with the most careful antiseptic precautions. As they usually die on the following day, we injected immediately on the same day the infundibulin. It was given by the jugular. In all cases sugar appeared in the urine. However, Nishi has shown that removal of adrenals is followed by hyperglycemia.

(3) *Splanchnicotomy.*—In cutting both splanchnics in the cat we followed the procedure of Schultze.[1] The animals were etherized and the strictest antiseptic precautions followed. The abdomen was closed by suture and the animals placed in the cage until the next day. Then they were again etherized, jugular prepared and infundibulin injected. But at no time afterward did we observe any sugar in the urine. Pollak[2] in a classification of the glycosurias found that adrenalin produces sugar in the urine after splanchnicotomy, being an agent which stimulates the terminals of a sympathetic nerve. The glycosuria of caffein does not ensue after splanchnicotomy.

[1] *Archiv. für Experimentelle Pathologie und Pharmakologie*, Band 43, p. 189.

[2] *Archiv. f. ex. Path. u. Pharmakol*, 1909, Band 61, p. 376.

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According to Macleod, curare does not cause any sugar in the urine after section of the splanchnics.

As section of the splanchnics arrests glycosuria we must consider it due to an action of infundibulin on the diabetic center in the medulla acting through the splanchnics on the glycogen of the liver. If the sympathetics influence the adrenals, who then actuate the glycogen in the liver, is a question not decided by these experiments.

Stimulant of Unstriped Fibers.—Dale[1] used a 5 per cent. acid decoction of the fresh posterior lobes of ox pituitaries. He found vaso-constriction of the pulmonary arteries on perfusion of lungs, which does not happen with adrenalin. It also constricted the coronary arteries; adrenalin dilates them. In perfused mammalian heart (rabbit) the ventricle beat becomes slightly slower and considerably more vigorous; later, with persistent retardation, it becomes weaker than before the injection. All these changes ensue after an atropinization, which excludes any action on the vagus. Hence the action on the heart beat is probably due to a direct effect on the heart muscle. It constricts the muscular capsule of the spleen. It also produced powerful uterine contractions. On the intestines, in dogs, he has seen the movements inhibited even when the splanchnics were cut. Isolated pieces of intestine contract,

[1] *Biochemical Journal*, Vol. IV, No. 9, p. 427, 1909.

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though but feebly, when pituitary extract is added. It is probable the inhibition just mentioned is due to intense anemia of the intestine which the drug produces by vaso-constriction. Hence the plain muscle of bladder and intestine contract in response to pituitary extract, but their sensitiveness is small in comparison to that of some organs. Ergotoxine annuls the motor effects of the sympathetic nerves and the action of adrenalin, so that the latter produces in the cat a fall of blood pressure and relaxation of the pregnant uterus instead of the customary rise and uterine contraction. But pituitary extract acts after ergotoxine on the arteries, contracting them and the uterine muscle.

He infers that the characteristic action of the infundibular part of the pituitary is to stimulate plain muscle fiber. There are no two active principles, the pressor and diuretic according to Dale.

Action on Intestinal Peristalsis.—Bell has shown that infundibular extracts have an action upon intestinal peristalsis in pithed rabbits, and he has advised its use in intestinal paresis after abdominal operation. Our experiments were made upon etherized rabbits. A brass cannula with a rubber balloon over its end was inserted into the small intestine, near the stomach end. It was attached to Albrecht's piston recorder and the normal movements were registered. Then the infun-

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dibulin was injected per jugular and the subsequent movements of the intestine noted. It had a marked action as is shown in Fig. 8.

Action upon the Uterus.—H. H. Dale, Bell and Hick have shown that infundibulin is a uterine stimulant. Our experiments were made upon etherized cats and rabbits. The abdominal cavity opened, the head in the Malassez holder elevated and the opened walls of the abdomen attached by hooks to a transverse bar. The pelvic cavity was filled with normal saline, heated to about the temperature of the body and kept so by frequent additions. This solution kept the uterus bathed. Then, as Cushny has advised, we attached two threads to the uterus and the other ends of the thread to a myocardiographic lever which registered the contractions of the uterus. It was a strong stimulant of uterine contraction, as Fig. 9 shows.

Prof. Von Frankl-Hochwart and Fröhlich in the rabbit found that pituitrin by the vein made the hypogastric nerve much more irritable, and also the uterus itself much more active, when the faradic current was applied to the hypogastric nerve. This uterine action is independent of blood pressure. Only the first injection is active as is the case in the action of pituitrin upon heart and blood vessels.

Bladder.—Von. Frankl-Hochwart and Fröhlich[1] used pituitrin. In cats and dogs pituitrin ex-

[1] *Wiener Klinische Wochenschrift*, 1909, p. 982.

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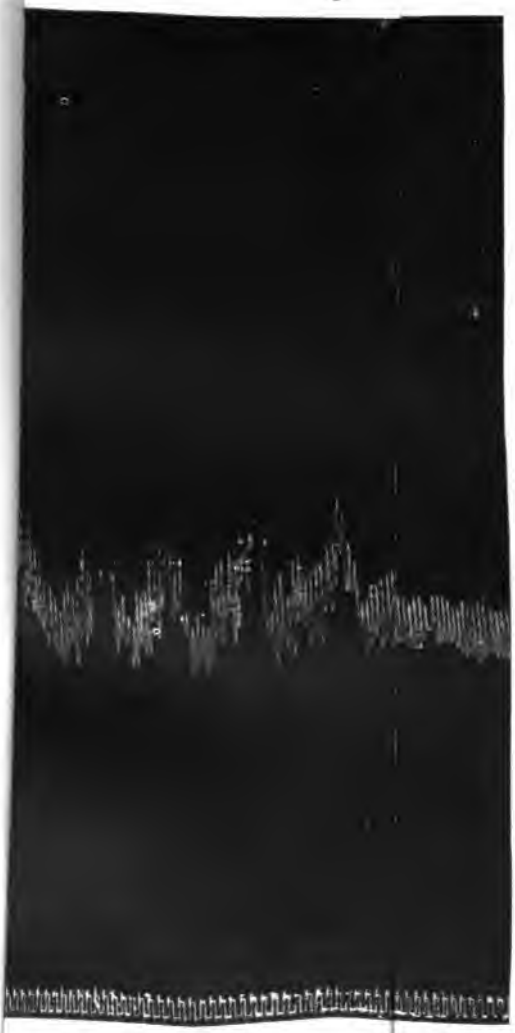

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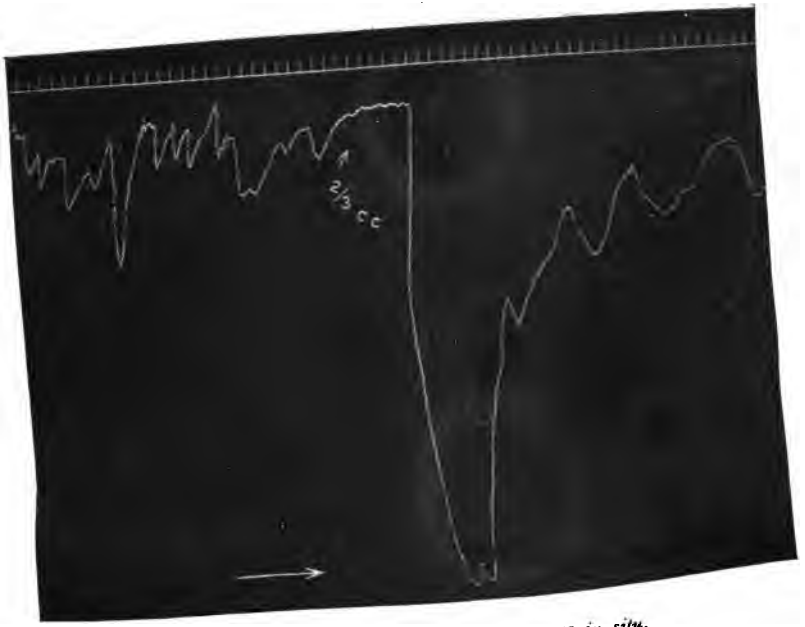

FIG. 9.—Effect of infundibulin on uterus *in situ*.

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cited the muscle of the bladder to a great degree and also considerably increased the excitability of the motor nerves of the nervus pelvicus as measured by the distance between the coils of a DuBois inductorium. They used it intravenously. Before the injection, the bladder contracted when the nervus pelvicus was irritated with the secondary coil at 19 cm. But after the injection of 0.5 pituitrin the bladder contracted at 26. The action was marked and constant. We have repeated this experiment in cats. The nervus pelvicus was placed on Ludwig's shielded electrodes, and a hollow glass tube with a short arm bent at right angles was bound in the neck of the bladder. Then we used the weakest faradic current that would make the warm Ringer solution mount up the tube. It was 20 cm. After injecting one cc. of 20 per cent. extract of infundibular part of the gland irritation of the nerve causes an ascent of the fluid when the DuBois coils were separated 28 cm. We also attached the bladder to a water manometer, opening the abdomen and severing the ureters, then closing the abdomen except where the tube attached to the manometer was connected. In this way we had a registration of the movements of the bladder.

When the infundibulin was injected we obtained a marked vesical contraction (Fig. 10.) If, however, the nervi pelvici were cut then infundibulin had hardly any effect, a slight

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increase at times of the contraction of the bladder. These experiments prove that infundibulin mainly excites the bladder by an action on the central nervous system.

In acromegaly there are bladder troubles, perhaps due to hyperhypophysy, or pressure on a vesical reflex center of 2″ order in locus niger.

Action on the Pupil.—W. Cramer[1] noted that extracts of the posterior lobe of the pituitary body of the ox produced a distinct dilatation of the pupil of the enucleated eye of the frog. The principle is distinct from that body in the pituitary which produces diuresis. Ott and Scott[2] found that the pituitary in the rabbit dilates the pupil after removal twenty-four hours previously of the superior cervical ganglion. It was used locally, by the jugular, and subcutaneously. In the normal eye no effect ensued. Pituitrin has the same effect, showing it is the infundibular part that dilates the pupil.

Von Frankl-Hochwart and Fröhlich found by intravenous injection of pituitrin a narrowing of the pupil.[3]

Temperature.—Mairet and Bosc have shown that pituitary extracts when injected elevate the temperature. Narbut found after removal of the hypophysis a lowering of the temperature on the day of the operation and a marked

[1] *Quarterly Journal of Experimental Physiology*, Vol. I, p. 187, April, 1908.

[2] *The New York Medical Journal*, Dec., 1908.

[3] *Wiener Klinische Wochenschrift*, p. 982, 1908, July 8.

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sinking of it before death. Vassale and Sacchi also noted a lowering of temperature after removal of pituitary. Injections of the hypophysis in these cases elevated the temperature.

Cushing found in animals suffering from hypopituitarism a rise of 2° to 4° C. by the injection of the boiled pars anterior.

After a partial removal of the pars anterior and an entire removal of the posterior lobe the temperature of the body just before the death fell to 63.5° (Cushing). We have seen the temperature fall to 94°, in monkeys after destruction of the pars anterior by the operation of Paulesco.

Removal of Pituitary.—In 1886, Horsely first made experiments for the removal of the hypophysis on two dogs. They soon died without any special disturbance. During the life of the animals he noted an increase of the excitability of the motor centers. A weak electric irritation of them caused unusually strong clonic cramps of the whole body. Dastre removed the pituitary, but the animals did not survive the operation. Gley also removed the hypophysis.

Marinesco operated on cats, which lived from one to eighteen days. The result was a great amount of wasting of the body, although artificially fed.

Vassale and Sacchi[1] operated on dogs and cats, and the longest time they lived was four-

[1] *Rivista sperim di Freniatria*, XVIII, 1892. *Ibid.*, XX, 1894.

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teen days. The symptoms mere apathy, motor troubles, rigidity of the back, somnolence, vacillating gait, dyspnea, anorexia, and polyuria. The dogs also rapidly lost flesh, and had tonic and clonic cramps with fibrillary contractions. Injection of pituitary extract temporarily made the symptoms better. The constant low temperature was marked, but after the injection of pituitary extract it returned to normal. After the effect of the injection had passed off, the temperature sank and at the same time the general state was worse. Caselli operated on 56 dogs and cats, producing extirpation, and came to the conclusion that the pituitary was a helping organ to the thyroid. The operations were made through the mouth, boring through the base of the skull. The hypophysis was destroyed by a sharp spoon, thermocautery or through chemicals.

Caselli found that complete removal of the functions of the pituitary caused at first slowing of respiration, acceleration of pulse, then depression of the psychical faculties, motor troubles with curving of the spine, spastic gait without tonic or clonic contractions, convulsive attacks, progressive cachexia, coma and death. In partial lesion of the hypophysis, in adults, you have the same symptoms as after total ablation, but these symptoms, corresponding to the functional insufficiency, gradually disappear and the animal passes into a subnormal state compatible with life. Psychical

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depression persists. In animals which are growing, the functional arrest of the hypophysis prevents their normal growth. The extirpation of the hypophysis modifies the course of tetania parathyreopriva, the tetany ceases after a short time and paralysis ensues, followed by coma and death in forty-eight hours.[1]

Friedman and Maas arrived at the conclusion that total extirpation of the pituitary was not incompatible with life. Monaco and Van Rynberk arrived at the same conclusion. Pirone operated on dogs, making partial and total hypophysectomies, and considered that the motor troubles, the apathy, psychic depression, rapid wasting, cachexia and death were due to pituitary insufficiency. He made some urinary analyses on the operated animals, and found an augmentation of urea and extractives. Gatta made some experiments and arrived at the conclusion that the hypophysis is indispensable to life.

Paulesco[2] arrived at the gland by means more adequate to remove the entire gland than previous observers who probably did not remove the whole gland as they operated either by way of the base of the skull or by the vertex. Paulesco freely removed the temporal bone on both sides, incised the dura mater, then he elevated the brain on one side by a retractor until the reddish yellow pituitary was seen

[1] *Caselli, Studi anatomici esperimentale sulla Fisiopathologia Della Glandola pituitaria*, 1900.

[2] *L'Hypophyse du cerveau*, 1908.

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lying in the sella turcica. Then it can by a small curette be easily shelled out, and the brain restored to its normal position and the wound closed. On the first day after the operation the animal had no bad symptoms, but on the second day they showed lassitude and died without any clear reason.

Paulesco states that the mere separation of the pars nervosa from the infundibulum has sometimes proved as quickly fatal as the actual removal of the gland.

Fichera (1906) and Gemelli[1] state that removal of the hypophysis is not followed by a fatal result. It is probable that they did not remove the whole gland, or the few cells in the pharyngeal pituitary of Haberfeld compensated.

Masay[2] has tried to produce pituitary insufficiency, that is, a lessening of the functions of the gland by preparing an anti-serum by intraperitoneal injection of a guinea pig with an emulsion of a dog's pituitary at intervals of two days. After five injections he collected the blood of the guinea pig, centrifugalized it and injected the serum (about 10 cc.) subcutaneously in the dog. After two or three of such injections the dogs lost flesh, had muscular weakness, especially of the posterior extremities, also changes in the skeleton and histological changes in the pituitary from a true cachexia hypophysipriva.

[1] *Folio Neuro-Biologica*, Nov., 1908, p. 167.
[2] *L'Hypophyse*, 1908.

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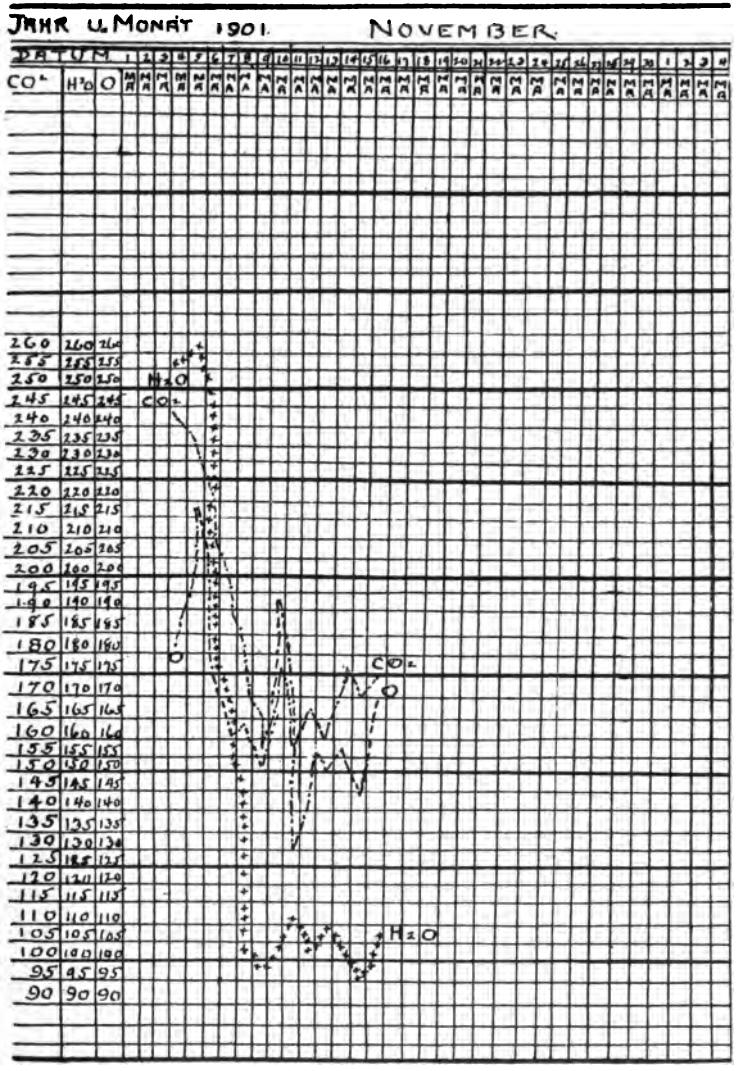

FIG. 11.—Dog—destruction of hypophysis cerebri; curve of water and CO_2 exhaled and of oxygen absorbed (Von Bechterew).

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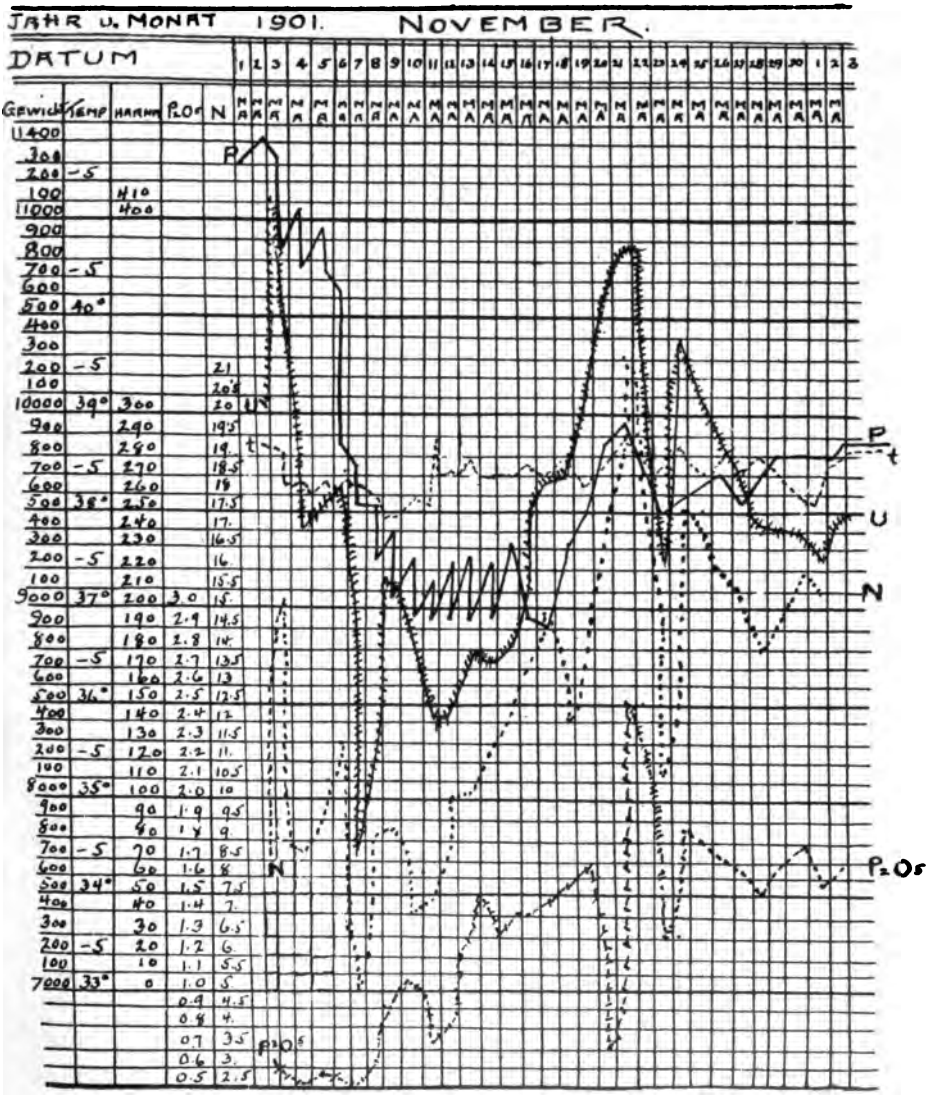

FIG. 12.—Dog—destruction of hypophysis cerebri; curves of P_2O_5 and nitrogen in urine and quantity of urine; t, curve of temperature; p, curve of weight of body; u, curve of urine (Von Bechterew).

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Cyon[1] holds that the pituitary gland contains several substances, one of which acts on the vagus, increasing its force and slowing its rate, acting like muscarine. He also saw the rise of blood pressure. His results have been contradicted by several observers. An antitoxic function of the hypophysis has been ascribed to it by Guerrini, Gemelli and Thaon.

Narbut (1909) in Bechterew's laboratory found on extirpation of the hypophysis a fall of temperature on the day of operation, which he thinks was probably due to injury of the tuber cinereum. Dr. Sakovic has shown that lesion of the tuber reduces the temperature. Narbut noted a marked sinking of the temperature before death (Fig. 11). He also noted after removal of the pituitary an arrest of growth in the anterior and posterior extremities and a partial want of growth in the skull.

The excretion of phosphorus and nitrogen was increased both absolutely and relatively, the excretion of the phosphates being increased threefold. The oxygen consumption and the CO_2 exhalation was decreased. The water exhaled was decreased (Figs. 11 and 12).[2]

Cushing, Crowe and Homans found that Gemelli's results were due to an incomplete removal of the gland. Cushing found that young animals, puppies, after hypophysectomy, do not have cachexia hypophyseopriva until thirty-

[1] *Die Gefässdrüsen*, 1910.

[2] Bechterew, *Die Funktionen der Nervencentra, Zweites Heft*, 1909, p. 1219.

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six hours to two weeks or so after the operation; with a transient glycosuria, with or without polyuria, the animal is normal in appearance. Then inactivity with a little stiffness and unsteadiness of gait is seen, lower temperature, awkward arching of back with incurvation of tail. There is a slow pulse and respiration, irregular muscular contraction, often snapping of the jaws, coarse shivering movements like in tetany. The animal is lethargic, indifferent to his surroundings, becomes comatose, slow pulse and occasional diaphragmatic respiratory movement. The temperature falls to 20° C., or lower.

In the hypophysectomized animals there were striking changes in thyroid and testis.

In the removal of the pars posterior, although some fragments of pars intermedia are left, there is no post-operative alteration in blood pressure, or in urinary secretion. In partial removal of the anterior lobe, the animals remain undersized, acquire no secondary sexual characteristics, have a tendency to hypotrichosis, and have subnormal temperature. In several adult males after a partial hypophysectomy of the anterior part there is a loss of spermatozoa, absence of mitosis and other peculiar changes in the spermatogenetic epithelium and certain alterations in the interstitial cells of Leydig. Histological changes are seen in the islets of Langerhans.[1]

[1] *Am. Journal of Medical Sciences*, April, 1910, p. 473.

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Crowe, Cushing and Homans[1] confirm Paulesco's work, that the pars anterior of the hypophysis is necessary to life. They show that Von Cyon's views (previously contradicted) are incorrect about the effect of mechanical irritation of the pituitary affecting the circulation or respiration. They observed no effect. Removal of posterior lobe produces no cachexia hypophyseopriva. Separation of the hypophyseal stalk, owing to circulatory disturbances, is comparable either to a partial hypophysectomy or to a total removal with immediate reimplantation of the excised tissue elsewhere in the body. The gland becomes reattached and the pathways for posterior lobe secretion supposed to traverse the pars nervosa on its way to the infundibular cavity may become obstructed by the scar leading to an accumulation of hyaline material within the channels of the pars nervosa. We have seen destruction of the pars anterior in the monkey produce death in 4 days.

Injections of Pituitary.—Intraperitoneal injection of extracts of the hypophysis according to Delille acts as follows: In small doses the repetition of injections for 3 to 4 days causes congestion and hyperactivity of the pituitary, the eosinophile cells are very much greater, the extra-cellular colloid was abundant. After 10 to 15 injections the eosinophile cells are less, the basophiles relatively abundant, little

[1] *Johns Hopkins Bulletin*, p. 127, May, 1910.

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extracellular colloid and a considerable quantity of chromophobes, there is no congestion. These facts have been confirmed in the main by Hallion, Alquier and Guerrini. Under the influence of injections of the whole hypophysis the adrenals double in weight, there is a diffuse cortical hyperplasia. The intraperitoneal injections seem to stimulate the adrenal secretion. The pituitary injections cause remarkable changes in the thyroid which is poor in large vesicles; there is little colloid, which finally disappears. At the periphery of the thyroid the large vesicles are nearly empty. The injections produced no effect upon the ovary or testis of a rabbit treated for more than a year. She was able to fecundate. In small doses it produces slight congestion of the liver and a granular fatty degeneration at the periphery of the lobule. The spleen did not show any changes. The kidneys were slightly congested; the glomerulus was always increased in size.

Extracts of the posterior lobes cause the same results as the whole gland. Extracts of the anterior lobe cause a slight hyperactivity of the hypophysis and do not change the adrenals. The thyroid by injection of the pars anterior shows a state of hyperfunction, the colloid is very abundant, and the large vesicles are very numerous. The anterior part causes the same lesions as the whole gland, but the lesions are less marked. The spleen is a little congested. The islets of Langerhan's are also congested.

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Parhon and Golstein found the following changes by the injection of the hypophysis: thyroid normal, *atrophied seminiferous tubules*; no change in ovary, adrenals enlarged and in a state of hyperplasia, fatty liver, spleen normal, and parenchymatous lesions of the kidneys.

G. Franchini[1] arrived at the conclusion from numerous experiments.

(1) The extract in rabbits only exceptionally causes glycosuria.

(2) The extract of the hypophysis causes, besides a toxic action, on rabbits and guinea pigs, an especial action upon the intestinal canal producing ulceration and hemorrhages.

(3) The greatest toxic activity is by the vein, but it can also ensue by subcutaneous or gastric exhibition. The act of digestion in vitro partly weakens the toxic action.

(4) The glandular part isolated from the pars intermedia produces only slight disturbances. If the pars intermedia is combined with it then it is toxic. The infundibular part isolated from the pars intermedia has an especial action upon metabolism and an action upon the blood vessels and the organs of abdomen and the pelvis.

(5) The infundibular part isolated from pars intermedia contains a substance which dilates the frog's pupil. This dilation is not produced by the anterior lobes, but by the pars intermedia and in a much less degree than by the

[1] *Berliner Klinische Wochenschrift*, 1910, p. 723.

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infundibular part. The serum from animals who have received injections from the extract of the posterior lobe produces dilated pupil. The serum from animals injected with extract of the isolated anterior glandular part isolated from the pars intermedia very seldom causes dilation of pupil, but if the pars intermedia is combined with the glandular anterior part the dilation of pupil is more frequent.

Cushing, Crowe and Homans[1] found after repeated injections of the posterior or infundibular lobe that there was loss of weight, extreme degree of hepatic degeneration and necrosis, subsequently found under other experimental conditions. This same lesion with no accompanying histologic changes in the kidneys has been found in a number of hypophysectomized animals *without* injections.

The subcutaneous administration of the pars anterior caused no such disturbances even when given daily over three months. Hence Cushing used the pars anterior as a means of tiding over periods of threatened cachexia hypophyseopriva in cases of almost total hypophysectomy. He also used the pars anterior to produce hyperpituitarism.

Action of Pituitary on Metabolism.—Malcolm[2] studied the action of the pituitary on the excretion of inorganic substances.

Nitrogen.—The dried glandular portion of

[1] *Bulletin Johns Hopkins*, May, 1910.
[2] *Journal of Physiology*, Vol. XXX, 1904, p. 270.

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the pituitary orally caused a slight retention of nitrogen; the dried nervous portion had a similar effect. The fresh entire gland increased the output of nitrogen.

Phosphorus.—The glandular portion caused a retention of phosphorus, while the nervous part caused a loss followed by a retention.

Calcium and Magnesium.—Both dried glandular and dried nervous part increased the output of calcium (on a calcium-rich diet); while the excretion of calcium in the glandular case was accompanied by an increased output of magnesium (in the feces at any rate), the nervous was not, or not to the same extent, so accompanied. This points to the nervous portion having a katabolic action on the bony tissues.

Thompson and Johnston[1] found the injection of the entire pituitary to lead to loss of weight by stimulating metabolism, increasing the nitrogen, urea and phosphorus in the urine.

Sandri observed no effect upon the growth of young mice from a two months' feeding of the pars anterior of beef pituitary, while those fed with posterior lobe showed a notable arrest of development.

Cushing states that repeated daily injections over long periods of the pars posterior leads to progressive emaciation, often with marked degenerative changes in the spleen and central necroses in the liver. Similar results of auto-

[1] *Journal of Physiology*, 1905, p. 889.

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intoxication were not uncommonly seen after operative removal of the gland.

Repeated daily hypodermic injections of the anterior lobe caused loss of weight, which has been seen by Casselli and others.

H. Salomon by feeding healthy men with large quantities of pituitary tablets found no increase of the respiratory gases.

Franchini[1] noted great changes by pituitary in metabolism, especially in the inorganic part. There is a great deficiency of calcium and magnesium and, to a small degree, also of phosphorus in the body. In the circulating blood, however, there is an increase of calcium and magnesium.

Metabolism in Acromegaly.—A. Schiff, of Vienna, found that the giving of hypophysis to an acromegalic caused a slight increase of nitrogen excretion; the quantity of phosphorus, especially by the intestine, was increased.

We may conclude that pituitary decreases the phosphates in the urine and increases them in the fecal matter. Infundibulin increases the excretion of calcium by the intestine and of magnesium by the urine. The nitrogen excreted is increased.

Magnus Levy in a case of acromegaly found that pituitary did not increase metabolism at all, or not to any important extent.

Parhon[2] has observed in acromegaly that tablets of pituitary caused an augmentation of

[1] *Berlin Klin. Woch.*, 1910, p. 723.
[2] Presbeanu, *Thèse*, 1909.

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the phosphates and a retention of calcium salts.

Tauzk and Vas examined the excreta and injecta for 8 days of an acromegalic and showed that the weight of the body augmented. Nitrogen and phosphorus were less in the excreta, while the salts of calcium were eliminated in more considerable quantity compared with those injected.

Moraczewski found in a case of acromegaly a retention of chlorine, nitrogen, phosphorus and salts of calcium. Audenino in studying two cases of acromegaly found in the first period a loss of nitrogen, which disappeared later. There was also an increase in the earthy phosphates. In the one case calcium was retained, in the other eliminated in a great degree.

Parhon from an analysis of urine in acromegaly found a constant retention of phosphorus, the urea often diminished.

The elimination of phosphoric acid was diminished.

Franchini studied three cases of acromegaly. He found in one a retention of N and CaO and MgO and a loss of P_2O_5, and a less marked retention of Cl. In the second case he noted a retention of N and Cl and a loss of the three other bodies. He noted an augmentation of elimination of calcium by the urine and a decrease of its elimination by the intestine.

Miller and Edsall found in acromegaly a marked retention of N, phosphorus and calcium.

[1] *Medical News*, 1903.

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Parhon cites Silva who observed in acromegaly a marked retention of nitrogen, increased elimination of sulphates and chlorides, while the phosphates were nearly normal.

It can be inferred from a study of the urinary excretions of acromegalics and when pituitary is given to them, that the excretion of nitrogen is less, that the phosphates are sometimes increased, at other times decreased, that calcium in the majority of cases is less, although in some experiments there was an increase of calcium in the urine, and a decrease of it by the intestines.

Growth.—Shäfer has made some experiments with white rats, feeding them with powdered anterior lobe of the pituitary, then weighing them and comparing their weight with that of control rats of the same litter. There seemed to be an increase of weight in those fed with the anterior part of the pituitary.

We have observed a great loss of weight in rabbits by subcutaneous injection of the hypophysis when continued for a few weeks. Cushing has also observed a loss of weight by the injection of the whole pituitary or of the infundibular lobe alone.

Schäfer[1] thinks the pars anterior is probably related to the growth of the cartilages, bones, and connective tissue in general, due to hormones. The function of the pars intermedia is to produce a colloid material which contains

[1] Croonian Lecture, *Proceedings of the Royal Society*, B, Vol. 81, 1909. "Functions of the Pituitary Body."

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the active principle acting upon heart, blood vessels and kidney.

Aschner has removed the hypophysis in a young dog and compared it with a dog of the same brood. The dog without the hypophysis was stunted in growth. He holds that the hypophysis is not necessary to life and that its absence produces dwarfs. This is supported by post-mortems in the case of dwarfs.[1]

Relation between the Glands.—Fichera found after castration in roosters that the weight of the anterior part of the pituitary doubled with an increase of eosinophile cells. This also held good for rabbits and oxen. Marenghi found after extirpation of the adrenals in cats and rabbits an increase of the pituitary. Rogowitsch found a hypertrophy of the pituitary after removal of the thyroids. This has been confirmed by numerous observers, as Hofmeister, Comte, Herring and others.[2]

In castrates, the hypophysis is enlarged, as has been shown by Fichera, Cimoroni, Tandler and Gross. This hypertrophy is due to an enormous increase of the chromophile cells which are a little larger than the normal ones.

Comte, Mulon, Von Erdheim and Stumme have shown the changes in pituitary during pregnancy while in acromegaly there are changes in the genitalia. The thyroid when ablated produces an arrest in the growth of the bones.

[1] *Wiener Klinische Wochenschrift*, p. 572, 1910.

[2] Oppenheim's *Handbuch der Bio-Chemie*, Band 3, erste Hälfte, p. 342.

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Hinsdale examined the records of 57 cases of autopsies of acromegalics; 15 times the thyroid was enlarged, 11 times it was atrophied, and 12 times it was normal.

The persistence of the thymus has been noted many times in the autopsies of acromegalics. The thymus and the chromaffine tissue also have a relation to the genital glands.

In myxedema and cretinism the hypophysis is enlarged, as has been shown by Ponfick, Dolega and others.

Parhon and Golstein and Pepere found that extirpation of the parathyroids had an influence upon the hypophysis which enlarges and the chromophiles are very numerous (Fig 13).

Is Acromegaly a Hyperhypophysy?—Pierre Marie first pointed out that in acromegaly you have a disease of the pituitary and held it was due to a hypohypophysy. Tamburni and Benda believed it was hyperhypophysy, an excess of chromophile cells being present. Hochnegg, in a case of acromegaly which was the first case successfully operated on (1908), showed that a year after the operation the length of the fingers and the feet diminished. Here we have in man (as Alfred Exner has stated) a decrease where an operation produced hypohypophysy, which reduced the acromegalic hands and feet.

Since Hochnegg's first successful case of hypophysectomy for acromegaly, he has operated on two other acromegalics, and one of these showed a great similarity to the first case.

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FIG. 13.—A case of acromegaly (Bouchard).

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The menses which had stopped for seven years returned. An adenomatous tumor was removed, the great increase of pain present diminished, and the fat decreased. The hands and feet diminished in size. The third case was a woman thirty-four years old; her menses had stopped for three and one-half years, and she had marked symptoms of acromegaly. She died shortly after the operation. All three cases were adenomatous tumors.[1]

The enlargement of the pituitary during pregnancy means an hyperhypophysy, and a diminished function of the internal secretion of the ovaries. In both cases of recovery after Hochnegg's operation there was marked enlargement of the thyroid. Cushing observed a simular effect after a hypophysectomy in man.

The operation of Hochnegg's was the first experimental evidence in man to prove that acromegaly was due to a hyperhypophysy and not to hypohypophysy as held by Marie.

Cushing removed a part of the anterior lobe in man, and a post-operative reduction in the hands ensued. There are, however, cases of acromegaly without enlargement of the hypophysis, but minute changes in the hypophysis might be overlooked, or even small tumors, as in a case of Erdheim's, where with a normal hypophysis a small tumor was found beneath the sella completely separated from the pituitary.

[1] *Mitteilungen aus den Grenzgebieten der Med. und Chirurg.*, 1909, p. 620.

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Brissaud and Henry Meige were the first to conclude that giantism and acromegaly are the same disease. The appearance in youth is giantism and in the adult it is acromegaly. The age is the only difference. Halmagrand (1907) holds that hyperhypophysy causes giantism.

Launois and Roy (1904) hold that giantism corresponds to a hyperactivity of the pituitary before the union of the epiphyses and acromegaly to the same hyperactivity after the union of the epiphyses. Cushing states that hyperpituitarism in youth gives giantism; in adult life it is acromegaly.[1]

Sternberg arrived at the conclusion that in acromegaly it was chiefly the anterior part of the pituitary which was the constant seat of the lesions. A histological study of a series of tumors of the hypophysis has a common mark, an increase of the chromophile cells, cells which are supposed to be secretory cells. Hence, Borchardt arrived at the conclusion that there is a hyperfunction of the secretory elements of the anterior part of the hypophysis, as the cause of acromegaly, as Hanseman first stated, and later Tamburini, Woods Hutchinson, Gubler and Benda. Cagnetto found an increase of chromophile cells, as did Achard, Loeper and Lewis. Cagnetto in a case of tumor of the hypophysis without acromegaly found there was an absence of the chromophile cells in the

[1] *Journal Am. Med. Association*, July, 1909, p. 255.

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anterior part of hypophysis. The same was true in a case of Carbone. Hence we may infer that giantism and acromegaly are due to hyperhypophysy of the anterior lobe of the hypophysis and to a hypersecretion by the chromophile cells of the pars anterior.

If the posterior lobe is also diseased you have polyuria. We might add that glycosuria is due to the invasion of the posterior lobe by disease which is usually cancer or sarcoma.

Infantilism.—Meige's definition of infantilism is an anomaly of development characterized by the persistence in a subject having attained or passed the stage of puberty, of morphological characters belonging to an infant.

Marie believed that changes in the functions of the sexual glands were initial symptoms in acromegaly. A. Exner believes hyperhypophysy secondarily leads to loss of function of the sexual organs and amenorrhea. When the pituitary was removed in cases of tumor then the menses became regular.

The observations of skeletons of eunuchs by Lortet, by Ecker and by Pirsche show that human castrates have a retard of complete ossification of the long bones.

Sellheim, Bonnet, Becker, Poncet, Pirsche and Möbius, in the lower animals after castration, have shown the presence of active cartilages in the long bones of the extremities and particularly at the epiphyses, which normally are joined to the diaphyses. This fact explains the

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unequal development of the extremities in relation to the trunk, and also the unequal development of different parts of the extremities when compared among themselves.

Delille[1] ascribes hypohypophysy as the cause of pituitary obesity, associated with infantilism. He also makes an obesity due to a hyperhypophysy, which conduces to emaciation by the hyperhypophysy, and causes hypothyroidism and suppression of the activity of the sexual organs and thus indirectly produces obesity. Here we have a pluri glandular action concerned in the production of obesity. The bone changes, the obesity, hypertension in arteries, and polyuria are due to hyperhypophysy.

Alfred Exner and V. Gschmeidler have grafted several hypophyses into animals and found afterwards a very marked increase of fat in them compared with the ungrafted controls.

Tandler and Gross in cases of acromegaly found changes in the epithelium of the seminiferous tubules and in the interstitial cells of the testis and ovary. A. Exner remarks that it is difficult to state if the increased amount of hair and obesity is directly due to hyperhypophysy or is indirectly due to the hyperhypophysy action upon the interstitial cells of the testis and ovary, and in this way causing obesity and increased amount of hair. At the menopause when the ovarian interstitial tissue is lowered in function we have a beard develop,

[1] *Thèse pour le Doctorat*, May 13, 1909.

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and there is a more abundant growth of hair about the linea alba.

During pregnancy we have more hair in the same places and also in the majority of cases of obesity. We know that in pregnancy we have hyper-hypophysy. In the acromegalic after the removal of the swollen hypophysis, the absent menses return and impotency is lost. Here the interstitial cells of the sexual glands have an inhibition removed and recover their wonted activity. Hence A. Exner holds that the function of the ovary and testis is partly to regulate the sexual activity, the growth of hair and obesity and that this function is inhibited by increased activity of the pituitary.

The anterior part of the pituitary seems to be associated with growth of the body with fat metabolism, and sexual activity. Removal of the posterior lobe causes no apparent disturbance of the physiological balance of the body.

Boyce and Beadles, in a woman with a great amount of subcutaneous and peritoneal fat, weighing 84 kilograms, had a hypophysis nearly double in size and the augmentation of volume was only in the anterior lobe.

Fröhlich first spoke of a dystrophia adiposo-genitalis, where we have infantilism of the sexual apparatus accompanied with obesity. These patients are small in height, have a smaller amount of hair, and excessive obesity, with symptoms of pressure in the vicinity of the hypophysis.

Von Eiselsberg has operated on these cases

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described by Fröhlich where they had pituitary disease without acromegaly, removing a part of the hypophysis. After the operation the fat diminished, the sexual apparatus was aroused to awakened activity.

Cushing reports a case of a man aged 40 who became very fat with polyuria and transient glycosuria, with sub-normal temperature, slow pulse, who had on post-mortem a primary tubercle of the hypophysis.

Leman and Van Wart[1] reported a case of infantilism with an absence of the thyroid and a tumor of the hypophysis. The woman was white, her skeleton long. No axillary or pubic hair, no mammary development, uterus infantile, lack of ossification in the epiphyses, and X-rays showed an enlargement of the sella turcica. She was fed with thyroid but without benefit. Pituitary extract improved her, and she gained 15 pounds in weight, a pound per week.

Crowe, Cushing and Homans[2] have found that in dogs partial removal of the anterior lobe of the pituitary leads to a state of adiposity accompanied by a secondary hypoplasia of the organs of generation in adults or by a persistence of sexual infantilism in case the primary hypophyseal deficiency antedates adolescence. Polyuria, glycosuria, alterations in the skin and its appendages (such as edemas

[1] *Archives of Internal Medicine*. 1910, p. 519.
[2] *Johns Hopkins Bulletin*, p. 127, May, 1910.

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and hypotrichosis), the tendency to a subnormal body temperature and psychic disturbances are more or less frequent accompaniments, all of them symptoms which occasionally occur with states of adiposity and of sexual infantilism in man in company with certain pituitary body-tumors, states therefore which presumably are due to deficiency of the pars anterior.

Cushing and his co-workers have undoubtedly cleared up the question that the cases of infantilism with excess of fat and atrophy of genitalia, are due to hypopituitarism of the pars anterior. How much the interstitial cells of Leydig or the interstitial cells of the ovary according to the theory of Tandler and Gross play a part in infantilism is still to be worked out. Cushing has found changes in the Leydig cells of the testes of the dog.

It must also be inferred according to Aschner that hypohypophysy produces dwarfs.

Hence cases of infantilism may be divided into two classes: (1) due to direct action of hypohypophysy, (2) the other indirect due to the hyperhypophysy, action on the thyroid producing hypothyroidism and suppression of the activity of the interstitial cells of the testis or ovary. These are the cases of "pluriglandular insufficiency" of the French authorities.

Transplants.—Crowe, Cushing and Homans had four cases in dogs of total hypophysectomy with hypertrophic changes in the thyroid, but where rectus implantation of the pituitary pro-

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longed the life of the animals. In another dog they implanted in a cavity prepared, by inserting a silver ball in bone marrow for ten days, and then implanting the hypophysis from another dog. Four days after the transplantation the dog's hypophysis was removed; no symtoms ensued from the operation. The animal's life was prolonged over the usual period of three to four days by the transplantation of hypophyseal tissue. In an auto-transplantation into the cortex cerebri after a total hypophysectomy, the duration of life was prolonged for eighteen days, when he was killed.

Glandular transplants or injections of anterior lobe emulsions definitely prolong the life of animals after total hypophysectomy and likewise tide over periods of threatened cachexia hypophyseopriva in animals retaining anterior lobe fragments which temporarily may be physiologically insufficient. They noted in some of the hypophysectomies a marked polyuria with transplants even of the anterior lobe alone in the transplant. This polyuria disappears after extirpation of the transplant.[1]

A. Exner[2] has implanted hypophyses in young rats. Their weight was increased, due to an augmented length in part and to increased fat.

THERAPEUTICAL APPLICATION.

Shock. Intestinal Paresis, Uterine Contraction. —Burroughs Wellcome & Co's infundibular

[1] *Quarterly Journal Experimental Physiology*, 389, Vol. II, No. 4, 1909.

[2] *Zentralblatt für Physiologie*, Band XXIV, p. 387.

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extract kept the blood pressure in man elevated for twelve hours. Bell recommends it for shock, like Mummery, Lockhart and Symes.[1] This Wellcome extract of the infundibular lobe causes powerful contractions of pregnant, puerperal and menstruating uteri. Bell also found it had a marked effect upon intestinal muscle, and found it useful subcutaneously into the muscles of the forearm for paresis and distension of the bowel after abdominal operations. The vaporole extract can be boiled and thus sterilized, but must be injected into the muscles to avoid superficial sloughing from the local vaso-constriction. The dose may be repeated with an hour's interval. It acts better on paretic intestine than on the normal one.[2]

G. G. Wray[3] has treated post-operative shock with considerable success. He injected 1 cc. of Burroughs Wellcome & Co's. 20 per cent. infundibular extract into the deltoid muscle. The effect of the pituitary extract upon the small, feeble pulse was to make it large, regular and forceful. Its effect lasted about twelve to fifteen hours.

Dr. J. A. Henton White, in a puerperal case with pneumonia and a weak heart, used 12 minims of pituitary extract by injection into the buttocks to stop post-partum hemorrhage. The depression which ergot would cause was unsuitable in this case. The pituitary caused,

[1] *British Med. Journal*, Vol. II, p. 736, 1908.
[2] Bell, *British Medical Journal*, p. 1609 Dec. 4, 1909.
[3] *British Medical Journal*, 1909, p. 1745.

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after the grasping of the placenta, a violent contraction of the uterus. The pulse instead of being thready and uncountable soon acquired a full volume and good tension. The general condition was very good.[1]

Thumin recommends in excessive menstruation, due to ovarian disturbance or excessive desires dependent upon an increased activity of the ovary as in nymphomania and other psychoses, tablets of the hypophysis. It is known that the excessive secretion in acromegaly causes a cessation of menstruation and loss of sexual desire.[2]

Tachycardia and Hypotension in Arteries.—When as a result of hypohypophysy by the toxines of diphtheria, or those of endogenous origin, then the use of pituitary is of great value. Hypertension is an absolute contra-indication to the use of pituitary extract. In the use of pituitary you watch the pulse and pressure and also examine the urine and blood.

Delille states that the extracts of the anterior lobe do not produce an appreciable therapeutic effect. Delille gives each day 0.10 gram to 0.40 gram of the whole dried gland.

Hallion and Carrion have seen a venous injection of pituitary extract in the dog produce an intense vaso-constriction of the thyroid as shown by the plethysmograph. This explains the good effects of pituitary medication in Basedow's disease.[3]

[1] *British Med. Journal*, 1910, p. 1282.
[2] *Berlin Klinische Wochenschrift*, 1909, p. 631.
[3] Halmagrand, *Etat. Actuel de l'Infantilism*, 1907, p. 58.

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H. Nageli and P. Vernier, of Geneva, have used 20–40 grams of powdered hypophysis extract with good results in low arterial tension.

Which Preparation of the Pituitary is the Best to Use in Tetany?—We have shown[1] in feline tetany that the pituitary gland given in distilled water subcutaneously had an effect at least equal to the calcium salts in alleviating the tetany after complete parathyroidectomy. As calcium has failed in several instances to cure tetany in man it is necessary to seek other agents to combat the disease.

Professor Pal, of Vienna, reports[2] a case of severe tetany in a boy. He gave pituitrin and the tetany disappeared in twenty-four hours, while the other symptoms retrograded. We have made experiments with pituitrin in feline tetany and find it has some effect which is, however, quite fugitive. We then tried the infundibular extract of Burroughs Wellcome & Co. (20 per cent.). It had a much more prolonged action than pituitrin, even when we gave the latter in ounce doses subcutaneously. But neither pituitrin nor infundibular extract had the continued power that the whole gland exerts. We used all these preparations subcutaneously. As the boiled filtered infusion of the whole gland can not be readily used we would recommend as the next best preparation the 20 per cent. infundibular extract of Burroughs

[1] Ott and Scott, *New York Medical Journal*, Dec. 10, 1908.

[2] *Wiener Klinische Wochenschrift*, July 8, 1909, No. 27, p. 983.

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Wellcome & Co. by intramuscular injection, in doses of 1 cc. three times a day. It should not be used subcutaneously, as it might cause some necrosis of the skin by the vaso-constriction. As infundibular extract is not very poisonous, it can be used oftener than three times a day if the conditions necessitate it.

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THIRD LECTURE—THE CORRELATION OF THE ACTION OF GLANDS WITH AN INTERNAL SECRETION.[1]

Gentlemen: The functional relations between the different internal secretions may be synergistic, supplemental and antagonistic. The active substances of the glands are necessary to the normal action of the nervous system, the circulation, metabolism and the growth of the tissues. Glands with an internal secretion are connected with the circulatory and lymphatic system, for the reception of materials from the blood and lymph and the ejection of their secretions into them. The removal of one of these secretions injures the whole organism and especially the bones and nervous system, when the full growth of the body has not been accomplished. It is not easy to definitely state the effect of the removal of a certain gland with an internal secretion, because it stands in a many-sided relation to the other glands with a similar secretion; you have a pluriglandular action. The absence of the thyroid causes idiocy; of parathyroid, tetany; of thymus, apathy; of ovary and testis, a change in the whole psychical condition. In anencephaly and hemicephaly the adrenals are small or absent. In the human fetus or the new-born they are normally of enormous size. In this defective development of the

[1] Lecture delivered in the Course on Physiology, Medico-Chirurgical College, 1909–1910.

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brain it is not the medulla but the cortex of the adrenal which is wanting. There is a remarkable relation between the growth of the brain and the adrenals. I might state that it will be necessary to repeat many facts noted in the preceding lectures. I will first speak of the action of glandular extracts upon the nervous system and will explain to you what chromaffine substance is.

Chromaffine tissue is a tissue which stains readily with chromic acid or its salts. This tissue is found mainly in the medulla of the adrenal, in some cells of the sympathetic ganglia, in the cells of the carotid gland, and in the lower animals a collection of cells at the point of division of the abdominal aorta. Such collections of cells containing chromaffine tissue have been called, by Kohn, paraganglien.

Swale Vincent[1] found that an extract of the abdominal chromophile body of the dog had precisely the same powerful effect upon blood pressure as an extract from the medulla of the adrenal. He stated that there seemed no reason why the hypothesis that all the chromophile cells had an internal secretion might not be admitted though this process was more completely elaborated in the larger chromophile bodies and in the adrenal medulla.

Langley divided the sympathetic nervous system. The true sympathetic arises from the dorso-lumbar cord and is distributed to all

[1] *British Medical Journal*, 1910, p. 1151.

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parts of the body. The parasympathetic arises from the mid-brain, bulb and sacral part of the cord, and its chief nerves are the oculomotor, chorda tympani, vagus and nervus erigens.

Adrenalin only stimulates the terminals of the sympathetic nervous system; it does not affect the parasympathetic. Adrenalin acts upon a "receptive substance" interposed between the terminals and muscle tissue, according to Langley. Infundibulin acts upon the sympathetic and also upon the parasympathetic, as, for example, in the increase of the excitability of the nerves going to the uterus and bladder. Thyreoidin, active principle of thyroid, also acts upon the sympathetic nervous system and upon the vagus.

About one millionth of a gram of adrenalin elevates blood pressure.

In the case of the adrenalin we have a chemical messenger, a hormone, for the sympathetic. The adrenal cortex contains choline. Klose and Vogt from experiments upon 54 dogs where the thymus had been extirpated noted a slight alteration in the psychical condition, apathy, and after 4 to 14 months the animal had a "cachexia thymopriva," "idiotia thymica," or idiocy.

Removal of parathyroids decreases the galvanic excitability of the nerves. Falta remarks about the attempt to explain tetany after parathyroidectomy by a deficiency of calcium that it would be very wonderful when so com-

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plicated an affair could have an explanation so simple. Removal of thyroid increases the galvanic excitability of nerves.

Action on the Blood.—The blood is the receptacle of all the internal secretions, a vehicle for all the hormones. The thyroid stimulates the formation of erythrocytes and mono-nuclear leucocytes. Thyreoidin causes a disappearance of the eosinophile cells (Falta).

The ovary increases the number of red corpuscles, but not their content of hemoglobin.

The liver and spleen regulate the richness of hemoglobin. The insufficiency of the thyroid secretion diminishes the number of the red corpuscles, the amount of hemoglobin and often produces an excess of leucocytes.

Adrenals on the Blood.—The majority of cases of Addison's disease have a deficiency of corpuscles. Adrenalin or adrenal extract excites the formation of all varieties of leucocytes and diminishes the red corpuscles. Adrenalin produces a leucocytosis, especially of the polynuclear neutrophiles and greatly diminishes the eosinophiles (Falta).

Of all the internal secretions the adrenal is the only one which is able in certain conditions to decrease the red corpuscles in a constant and progressive manner. As a rule it may be stated that nearly all the internal secretions favor the formation of blood. The hormones of the internal secretions are a primary agent in the

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regulating mechanism of the manufacture of blood.[1]

PARATHYROIDS.

Viscosity.—The researches of Fano and Rossi have shown that removal of the parathyroid in the dog does not have any influence upon the viscosity of the blood. Removal of the parathyroid causes a disappearance of the eosinophile cells.

Blood Coagulation.—Salvioli believes orchitic extract retards the coagulation of the blood.

Prostatic extract according to Zapelli and Matozzi-Scafa in the dog retards coagulation. Prostatic extract is very toxic. They state that it has a paralyzing action upon the cardiac apparatus and the center of respiration, which I can confirm.

Infundibulin has no effect upon the blood. However, W. Zyembicki,[2] in tumors of the hypophysis, nearly always found eosinophilia.

Removal of pancreas causes a disappearance of eosinophile cells.

Action on the Circulation and Diuresis.—In considering the effect of some of the animal extracts on the circulation, it must be remembered that T. Kinoshita in Von Fürth's laboratory has found 0.01 to 0.03 per cent. of cholin in the pancreas, spleen, liver, kidney, duodenum, muscle and the lung of the cow.[3]

Roger has found a hypotensive substance in

[1] *Secretions Internes, par* Maurice Perrin, Paris, 1910.
[2] *Wiener Klinische Wochenschrift*, 1910, p. 719.
[3] *Pflüger's Archiv*, Band 132, p. 631, 1910.

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the adrenals like that in thyroid and hypophysis.[1]

Adrenalin and infundibulin both increase blood pressure; the adrenalin does it rapidly and it lasts only a short time; infundibulin does it slowly, but it lasts for some time. Adrenalin slows the heart to a marked degree, while infundibulin retards it only a little. After section of the vagi the heart is accelerated by adrenalin. Adrenalin stimulates the cardio-inhibitory centre in the medulla oblongata, infundibulin slows the heart even after section of vagi or previous atropinization which paralyzes the vagus, hence the cause of the slowing is seated in the heart itself. Adrenalin dilates the coronary arteries, infundibulin narrows them. Adrenalin contracts the renal arteries, infundibulin dilates them. Adrenalin increases the force of the heart muscle.

Thyreoidin, the active principle of the thyroid, accelerates the heart beat and the blood pressure is not elevated.

Jeandelize and Parisot found in a rabbit who was thyroidectomized in his youth that after a certain time there was arterial hypotension. The serum of the animal also lowered arterial tension. In thyroid insufficiency of man there was a lower blood pressure.[2]

Iodothyrin (1 grain) increased the flow of urine to a small extent. It also increased the volume of the kidney, although at the time the general

[1] *Compt. rend. Soc. de Biol.*, 1910. Tome 69, p. 160.

[2] *Journal de Physiologie et de la Pathologie generale*, 1910, p. 339.

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blood pressure was decreasing the heart-beat remained the same. The first injection of iodothyrin in the cat elevated for the moment arterial tension, but it soon fell. The heart-beat was increased.

Coronedi[1] confirms my results. He found the thyro-parathyroid secretion kept the secretory activity of the kidneys, adequate to the needs of the organism in dogs thyroidectomized. After thyroidectomy the kidney of the dog has a functional insufficiency.

Spinal cord (1/8 grain) had no effect on flow of urine; did not alter rate of pulse; increased blood pressure.

Prostate had no effect on urinary flow; did not alter pulse rate; increased blood pressure.

Ovary reduced flow of urine; did not alter pulse rate, but reduced arterial tension.

Spleen (½ grain) reduced urinary flow; did not alter pulse rate; lowered arterial tension.

Testicular extract (1/8) grain) did not affect flow of urine or pulse; increased arterial tension.

Bielow[2] found that the secretion of the corpus luteum lowered blood pressure and slowed the heart. He also calls the corpus luteum the "glandula lutea ovarii."

Mammary gland (1/50 grain) produces a slight increase of diuresis. The volume of the kidney increased at the time the blood pressure was falling, while the heart-beat was somewhat

[1] *Journal de Physiologie et de Pathologie*, 1910, p. 599.
[2] *Muenchener Medizinische Wochenschrift*, 1910, p. 1707.

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increased. In the cat the mammary gland extract increases the heart-beat and temporarily increases the general arterial tension, after which it falls considerably.

The parathyroid powdered extract (1/10 to 1/5 grain) at first decreases the volume of the kidney and then gradually increases it. The increase of the kidney volume is often so great that the registering pen cannot record it. The primary decrease of kidney volume is due to a temporary slowing of the heart. The subsequent increase of volume in the kidney is not due to any change in the rate of heart-beat, and the general blood pressure at the time fell slightly. As a diuretic, the parathyroids were the most powerful of all the gland extracts. With the nucleoproteid prepared according to Beebe's method by Dr. W. N. Berkeley the increase in the amount of urine was ten times that of normal. We found the parathyroids in a case of interstitial nephritis increased the quantity of urine a half pint a day.

Thymus slightly increased the flow of urine. It also augmented the volume of the kidney, although the pulse rate remained unaltered and the arterial tension was falling.

Lucien and Parisot found the thymus extracts lowered blood pressure. They think this is due to the lymphatic tissue in the gland and not the gland itself or the corpuscles of Hassal.[1]

The pancreas increased the flow of urine.

[1] *Zentralblatt f. Physiologie*, Band 24, p. 2401.

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The volume of the kidney was slightly increased, while the general blood pressure was decreasing, and the rate of heart-beat considerably increased.

After injection by jugular of pancreas the urine contained 1/4 per cent. of sugar, as shown by the fermentation and Fehling's test.

Schaefer, Houghton and Merril have shown that the pituitary extract (infundibular part) increased the flow of urine. The volume of the kidney was greatly augmented, so much so that the lever could not register at times. Infundibulin per jugular causes glucose to appear in the urine.

The renal cortex increased the flow of urine. The volume of the kidneys in doses of 1/50 to 1/25 of a grain did not change.

Adrenalin decreased momentarily the volume of the kidney, while the blood pressure rose and the heart was slowed. Afterwards the kidney volume was greatly increased.

All these agents, the renal cortex, pituitary extract, pancreas, parathyroid, mammary gland, thymus, iodothyrin and adrenalin, are diuretics. Gouin and Andouard found thymus in large doses produced diuresis in the calf. The above agents, except adrenalin, do not markedly increase general arterial tension, except for a moment, and then lower it. It is inferred that the very short rise of blood pressure does not produce the diuresis, which continues for a considerable time afterwards.

As the changes of arterial tension do not play

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any large part in the diuresis, it must be referred to an action on the renal epithelium itself.

Action upon Intestinal Peristalsis.—Adrenalin arrests it temporarily (Fig. 14), infundibulin accelerates it. Iodothyrin increases the frequency and extent of contraction. Parathyroid, mammary gland, spleen (Fig. 15), pancreas, prostate, thymus, parotid, brain and spermine (Poehl) increased the contractions.[1]

Action upon Movements of Bladder.—Adrenalin stops them temporarily, infundibulin increases them. If the nervi pelvici in the cat, which contain motor and (according to Langley) also inhibitory fibers, are cut then infundibulin has a very weak action. This shows it mainly causes contractions of bladder by stimulating the vesico-spinal center. As Von Frankl-Hochwart and Fröhlich have pointed out it increases the irritability of the nervi pelvici. I can confirm this.

Thyroid extract produced strong vesical contractions.

Parathyroid increased the contractions of the bladder.

Pancreas increased the vesical contractions normally and after section of the nervi pelvici.

Normally thymus increased the extent of the contractions of the bladder.

Ovary normally increased the extent of contractions of the bladder.

[1] Ott and Scott, Unpublished experiments, 1910.

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Parotid considerably increased the frequency of the contractions of the bladder.

Brain extract increased the frequency of the vesical contractions.[1]

Action upon the Uterus.—Adrenalin in unimpregnated uterus of the cat relaxes the uterus; in a pregnant uterus it causes contraction. Here the hypogastric nerve contains both augmentor and inhibitory fibers going to the uterus. Infundibulin stimulates the cat's uterus to a marked contraction[2] so does iodothyrin, parathyroid, mammary gland, spleen (Fig. 16), pancreas and prostate (Fig. 17). Thymus and spermine had some effect. Ovary had a very slight action on unimpregnated uterus.

Action upon Pupil.—Adrenalin dilates the pupil in rabbit with superior cervical ganglion excised and in large doses the normal pupil. Pituitary extract and pituitrin dilates the excised pupil of the frog, and the pupil in the rabbit on the side where the superior cervical ganglion is excised.

Iodothyrin dilates the pupil on the side where the superior cervical ganglion was excised; no effect upon normal pupil. The dilation was preceded by a slight contraction.

Parathyroid nucleoproteid on the normal eye dilated the pupil, on the side with excised superior cervical ganglion; it at first contracted and then dilated it. The mammary gland had no effect.

Thymus had no effect upon the pupil.

[1] Ott and Scott, Unpublished experiments, 1910.

[2] Ott and Scott, *American Journal of Obstetrics*, 1910, p. 766.

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Parotid and testicular extract contracted the pupil upon both sides, the normal one and the one with excised superior cervical ganglion.

The ovary had no effect.

Action on Temperature.—Narbut, like Vassale and Sacchi, in Von Bechterew's laboratory, found after removal of the hypophysis a lowering of the temperature on the day of operation and a marked sinking of it before death.

Cushing has shown that the removal of the anterior part of the pituitary lowers temperature to a great degree and injection of the pars anterior again elevates this low temperature.

Adrénalin increases temperature.

Infundibulin has a similar effect.

Glandular Glycosurias.—In 1889, Mering and Minkowski made a total extirpation of the pancreas and observed sugar in the urine.

Forsbach[1] has made some experiments, in which two dogs of the same kind and same brood had the skin, muscle and peritoneum of each united together by ligatures. Here an exchange of blood takes place by the newly formed blood vessels and an exchange of lymph through the communication of peritoneal cavities. He showed that many things, as iodine, sugar, strychnine, and so on, went from one animal to the other. If now in the living dogs the pancreas is extirpated in one, then the usual glycosuria did not ensue to the usual extent, and in many cases was very little. If, however,

[1] *Deutsches Medizinische Wochenschrift*, 1908.

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the depancreated dog was separated from the normal dog, then glycosuria took place to the usual extent in the animal without the pancreas.

Minkowski and Hedon found in dogs that if a transplant of a piece of the pancreas, the "processus uncinatus," is made under the skin of the abdomen and simultaneously or later the remainder of the pancreas and its duct be extirpated, the appearance of sugar in the urine was usually prevented, but ensued after removal of the piece of pancreas in the subcutaneous tissue. Pflüger ascribes the appearance of glycosuria after removal of the pancreas to injury of nerves in the duodenum. His view has been contradicted by many observers.

It has been inferred that in the cells of islets of Langerhans we have the internal secretion of the pancreas. Severe diabetes can occur without changes in the pancreas.

Opie studied very carefully the pancreas of five diabetics. In three he observed marked total hyaline degeneration of the islets. In two others the degeneration was less marked. Similar degenerations were not found by him in the pancreas of non-diabetics. In the diabetic cases the parenchyma of the acinus was more or less altered. Ugo Lombroso,[1] from a review of the literature of pathological and anatomical facts, states that the internal function of the pancreas can not be provided by only one of the tissues of the gland, be it acini or islets.

[1] *Ergebenisse der Physiologie*, 1910, p. 47.

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Lombroso,[1] from an analysis of experimental work upon animals, concludes that both epithelial tissue of pancreas, the acini as well as the islets, take part in the internal secretion.

Cohnheim has shown that if the pancreas, which contains a body not a ferment, and called by him the activator, is mixed with muscle extract in certain proportions, that the mixture is a marked glycolytic agent. His theory has been contradicted.

Adrenalin and infundibulin produce glycosuria, the former after section of the splanchnics; infundibulin has no effect after splanchnicotomy. After extirpation of adrenals, diabetic puncture fails to cause sugar in urine.

Parathyroid and pancreas in large doses subcutaneously in rabbits produce a slight glycosuria, 1/8 per cent. Extirpation of thyroid reduces the glycosuric action of infundibulin, pancreas and parathyroid. In some cases of dogs and cats sugar appears after extirpation of the thyroid alone.

It seems that the absence as well as the excess of the internal secretion of the pancreas conduces to glycosuria.

In thyroidectomized dogs Falta states that adrenalin produces no glycosuria. Underhill, however, finds that if the dose is large enough sugar appears in the urine.

The present theory of diabetes is that a glyco-secretory center exists in the medulla oblongata,

[1] *Ergebenisse der Physiologie*, 1910, p. 89.

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from which fibers run down the cervico-dorsal cord to the solar plexus and then in the trunk of the splanchnics to the liver cell. Falta states that high section of the spinal cord, or the withdrawal of the adrenals by section of its nervous connection with the diabetic center, leads to a very marked reduction of the amount of sugar in the blood, like when you extirpate the adrenals themselves. Fom the analogous effects of diabetic puncture compared with adrenalin injections, it is inferred that the sympathetic fibers actuate the formation of sugar in the liver *via* the adrenals (Schur and Wiesel). Normally diabetic puncture increases the amount of adrenalin in the blood.

Falta states that after bilateral section of the vagi the content of sugar in the blood is elevated. There was also a well marked increase and hypertrophy of the cells of Langerhans in 3 dogs who had their thyroid removed six months previously. These facts lead Falta to think that by the vagus and pancreas we have an inhibitory action, on the production of sugar and an increase of sugar by the sympathetic *via* the adrenals on the liver cell. By this checking action the level of the content of sugar in the blood is kept constant.

As Boruttau puts it, the adrenals produce a hormone which sets in motion glycogeny in the liver while the pancreas furnishes another hormone by its internal secretion which antagonizes the sugar driving function of the

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adrenals. Hence the diabetes after pancreatic extirpation is a negative pancreatic diabetes and a positive adrenal diabetes.

Irritation of the sympathetic in the neighborhood of the adrenals increases the amount of adrenalin secreted Adrenalin solution 1 : 1000,000 flowing into a vein (4.1 cubic centimeters per minute) produces adrenalin glycosuria according to Straub.

Pluriglandular Action.—Just as glands with an external secretion concur in taking up the work not accomplished by the others, and unite in the perfection of the products to be brought forth, in a similar way the glands with an internal secretion concur in the metabolites to be produced, a sort of physiological balance is maintained between the activities of the different glands in the wilderness of metabolism.

Klose and Vogt, from experiments upon 54 dogs in whom they extirpated the thymus, had the following results: in the first 2 to 3 months, their weight increased like in the control animals. There was slight alteration in their psychical condition, apathy, increased appetite, they were fat, the stage of adiposity. Then the weight sank more or less rapidly and this phase lasted 4 to 14 months. The animals were idiotic, "cachexia thymipriva" (iodiotia thymica); they had spontaneous fractures. Finally the animals died in a state of thymic coma lasting 5 to 8 days. Rachitis, osteomalacia and osteoporosis were present in the same animal.

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The common cause was a great want of calcium in the thymected organism. The cause of the deficiency of calcium and the idiocy is an acidosis. Klose holds that the thymus is the chief organ for the synthesis of nuclein.

The removal of the thymus permits the lower building stones of the organism, perhaps a great excess of the incombustible phosphoric acid to circulate in the blood. The acid dissolves the calcium salts, or holds them in solution. Artificially produced fractures do not unite with callus but only with connective tissue. The chief organ which substitutes for the thymus is the spleen. It acts after the phase of involution of the thymus.[1]

Worms and Pigache[2] found in thyroidectomized dogs and rabbits a disappearance of the thymus which was replaced by connective tissue.

Renon and Delille[3] have found that injections of the extract of the hypophysis cause a hyperfunction and very often hypertrophy of the adrenals. Inversely the hypophysis of animals treated by the adrenals have been found congested and in hyperactivity. Parhon, Hallion and Alquier, Renon and Delille are in concord about this result.

New researches by Renon and Delille tend to demon trate that it is only the extract of the posterior lobe of the hypophysis which causes a hypertrophy of the adrenals. The extract

[1] *Muenchener Medizinische Wochenschrift*, 1910, p. 874.
[2] *Compt. rend. Soc. de Biol.*, LXVIII, 32, p. 500.
[3] *C. R. Soc. de Biol.*, June 13, 1908.

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of the anterior lobe is without effect, but provokes a hyperfunction of the thyroid, while the extract of the posterior lobe has an opposite action upon the thyroid.

Tandler[1] holds that in the sexual glands we have (1) a generative part, and (2) a part devoted to an internal secretion. If you apply the X-rays to the testes, then the generative part is destroyed, but the internal secretion remains. The same result can be obtained to a certain extent by ligature of the vas deferens. I shall give you an abstract of Tandler's lecture upon this subject before the Royal Medical Society of Vienna.

Tandler, from an examination of the testes in about 20 cases of cryptorchids, found in all an absence of spermatogenesis, but regularly normal developed Leydig cells. The bilateral cryptorchid has the normal primary and secondary sexual characters, except he has azoospermia, otherwise he is a normal individual.

Nielsen examined the testes in 20 cryptorchids in the horse, and at no time saw spermatogenesis. These facts show the worth of the interstitial cells.

By these facts he has arrived at the conclusion that the interstitial cells are the parts of the testes concerned in the changes in the external form of the body. The interstitial cells in the ovary are those in the stroma of this body. The corpus luteum inhibits the internal secretion of the ovary. In the castrated female

[1] Wiener, *Klinische Wochenschrift*, 1910, p. 459.

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and in the pregnant one the hypophysis is enlarged, hence there is a relation between the ovary and the hypophysis. In the cow there is not seldom a hypertrophy and persistence of the corpus luteum reaching the size of a nut. In this condition the state of "heat" does not come on every 21 days. If, however, the corpus luteum is extirpated, then typical heat comes on in a few days. In woman, there is a persistence of the corpus luteum of pregnancy. At the same time, as a rule, ovulation is absent in the cyclical activity of the ovary. The same state of affairs persists after delivery, that is, the corpus luteum may be the cause of delayed menstruation during lactation. The interstitial cells of the ovary are concerned with the internal secretion of the ovary. The action of the interstitial cells of these sexual glands upon the form of the body starts in embryonic life. The dimensions of the body and the changes in the skeleton are conditioned upon the internal secretion of the sexual glands. We know that castration and hypoplasia of the sexual glands leaves the epiphyses unjoined. During pregnancy the persistence of the corpus luteum is inhibitory of an internal secretion of the ovary.

Loeb[1] holds that at a certain period of "heat" a few ovarian follicles rupture and become transformed into corpora lutea. In the early stages of their life the corpora lutea constitute one of the factors, initiating growth processes in the

[1] *Journal Am. Med. Association*, 1910, July 9, p. 166.

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uterine mucosa by means of an internal secretion. If pregnancy takes place the ovum adds a mechanical stimulus to the sensitizing action of the corpus luteum and a maternal placenta is produced. A foreign body placed in the uterus can do the same as the ovum. In this period the corpus luteum exerts a new function, it prevents the rupture of new follicles and prolongs artificially the period of the sexual cycle. Starling has shown that the dried embryo contains a hormone which by the blood stimulates the growth of the mammary gland.

The placenta according to Von Basch causes the growth of the mammary gland even when the nerves of the mamma are cut or even when the gland is transplanted. The mammary gland of the fetus often secretes milk, from the same cause in the blood of the mother.

Rapid development of puberty goes with early juncture of the epiphysis to the diaphysis and necessarily short bones.

Hypoplasia of the sexual glands, or late puberty of the individual, produces long bones. In mankind the earlier puberty of the femal compared with the male makes her bones shorter. Hence, early puberty in hot climates produces individuals short in stature, while late puberty of cold climates produces tall individuals.

The influence of the sexual glands is seen in the subcutaneous fat in castrates, at the menopause and in old age. The hypophysis is a regulator of the growth of the bones, especially

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in the promotion of their growth. The castrate becomes tall from the greater action of the anterior part of the hypophysis.

Nussbaum[1] found in frogs castration caused the secondary sexual characteristics to disappear if the operation was done in their youth. The pads on the thumbs disappear in the male. If you inject testicular material from the same species then they appear. Feeble nutrition plays no part here.

Hypofunction of the ovary produces changes in the hypophysis, which changes the growth of the skeleton.

As to the growth of fat connected with the sexual glands, we can speak of a hypophyseal fat.

As to the relation of the thyroid to the sexual glands, we must remember the sterility of the cretins, the genital disturbances in Basedow's disease, and the changes in the thyroid at the time of menstruation, during pregnancy and at the menopause.

Walter Edmunds has found that 10 grains of thyroid extract administered three times a day to rats will cause death in about twenty days from congestion and hemorrhage into the adrenals.[2]

Thyroid and Growth of Bones.—E. Bircher[3] studied the effect of thyroid tablets upon the growth of bones. He found the thyroid tablets

[1] *Pflüger's Archiv.*, 1909, Band 129, p. 110.

[2] Personal communication.

[3] *Archiv. Klin. Chir.*, Band 91, Heft 3, s. 554.

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lead to a more rapid calcification of the epiphyses of the bone. They did not (as expected) lead to an increase in the length of the bones.

Adrenals.—In the disease of the chromaffine tissue of the adrenals, or Addison's disease, we often have impotency and menstrual disturbances. In a case of Addison's disease, post-mortem sections of the testis by Kyrle showed especially a want of spermatogenesis, and changes in the interstitial cells. In a case of hypoplasia of the adrenals with an absence of the right adrenal while the left adrenal was small and flat and the cortex could hardly be seen, Schlangenhaufer found similar but much more developed changes in the testis. In the pseudo-hermaphrodites there is enlargement of the adrenals.

Hypertrophy of adrenals is seen during menstruation and pregnancy. Here the changes in the adrenals are probably the primary cause of changes in the ovary.

Hallion and Alquier have seen the prolonged ingestion of adrenals cause histological changes in the thyroid and adrenals. They found no lesions in the kidney, testis, liver or hypophysis.[1]

Ovaries and Adrenals.—F. Schenk[2] holds that adrenals, ovaries and testicles have a definite relation to each other. Castrated male or female rabbits have a hypertrophy of the adrenals and the hypertrophy is chiefly localized in their cortex.

[1] *Compt. rend. Soc. de Biol.*, 1910, Tome 68, p. 966.
[2] *V. Brunnsche Beiträge zur Klin. Chirurg. Bd.*, 67.

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Ovaries and Hypophysis.—E. Mayer[1] concludes that the hypophysis enlarges after castration and after diseases in which there is a partial or complete rest of the ovaries or testicles.

Alquier[2] finds after ovariotomy less marked histological changes in the hypophysis and thyroids than in animals which have been castrated. The changes in the hypophysis and thyroid are due to hyperfunction of these glands. As to the effect of removal of ovaries upon the adrenals the effects are yet doubtful.

Thymus.—The thymus and sexual glands are complementary glands, thus the persistence of the thymus in castrates and eunochoids. Persistence of the thymus is a sign of general want of maturity in the organism. In guinea pigs and bulls, removal of thymus causes the testes to greatly increase in size, hence it is probable that the thymus has an internal secretion which controls the growth of the testes.

Soli found in cocks that ablation of the thymus retards the growth of the testicles. If the cock lives until his period of copulation, then the testis attains its normal development. He holds that the thymus is in relation not only with the development of the skeleton, but with the regular and physiological development of the testis.[3]

Enlarged hypophysis inhibits the ovary and

[1] *Archiv. f. Gynekol.*, 1910, Band 90.

[2] *Gaz. d. hôpital*, No. 59.

[3] *Journal de Physiologie et de Pathologie générale*, 1910, p. 599.

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testis. Between the testis and ovary on one side and the adrenal and thymus on the other there is an atagonism.

Landau,[1] after removal of the adrenals, found no changes in the hypophysis, thyroid and ovary. Feodossjeff[2] after removal of the ovary found a marked hyperplasia of the cell elements of the adrenals.

Falta has made the most lucid explanation of pluriglandular action. His theories rest upon solid experimental work.

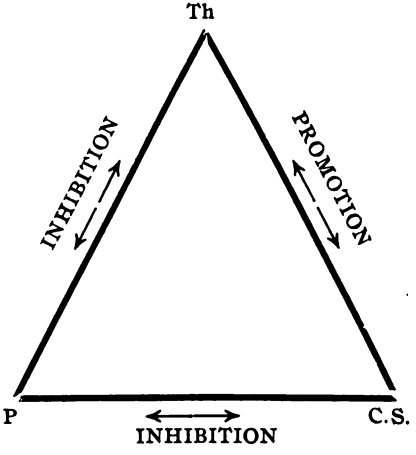

FIG. 18.

Th = thyroid. P = pancreas. C. S. Chromaffine substance. Between Th and P, as well as between P and C. S., there is a reciprocal inhibition; between Th and C. S., a reciprocal promotion of each other's functions. The inhibition is stronger than the promotion (Falta).

[1] *Experimenielle Nebennieren Studien.* 1908.

[2] From Landau's work.

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The following is an abstract of Falta's paper.[1] As Falta has stated, the removal of a gland with an internal secretion produces two results: (1) the direct action of absence of the internal secretion of the gland, and (2) an indirect action, by the disturbance of the metabolism in relation to the other glands, as, for instance, between the thyroid and pancreas there is inhibition against each other, between the pancreas and chromaffine tissue a reciprocal inhibition, while between the thyroid and chromaffine tissue there is a reciprocal promotion of activity. Thus, extirpation of thyroid leads by removal of the inhibition to hyper-function of the pancreas; the extirpation of thyroid by the removal of its power of promotion, to diminished adrenal action. On the other hand, increased hyperthyroidism by increased inhibition leads to relative insufficiency of the pancreas. Hyperthyroidism, through increase of the promoting influences, leads to increased adrenal action. Extirpation of the pancreas by the removal of its internal secretion directly prevents destruction of the sugar, indirectly to absence of an intense inhibition of the thyroid, a hyperfunction of the thyroid, which results in an increase of the metabolism of the proteids, fats and inorganic materials. If the pancreas's intense inhibition upon the chromaffine tissue is removed, there is a hyperfunction of the chromaffine tissue, with

[1] Eppinger, Falta und Rudinger, *Zeitschrift für Klinische Medizin*, 1908, pp. 1–52.

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consecutive, excessive, rapid mobilization of the carbohydrates. The promotion of the activity of the chromaffine tissues directly is by the removal of the intense inhibition of the pancreas on the chromaffine tissue, and indirectly by the removal of the inhibition of the pancreas on the thyroid, and thereby to increase of the thyroid promoting action on the chromaffine tissue, that is, the activity of the chromaffine tissue is greatly increased. In this way the well known intensity of pancreatic diabetes is explained, and the two theories of diabetes, one a disturbance in the destruction of sugar, the other, a disturbance in formation of glycogen; both may be right—due, according to the first theory, to removal of pancreas; the second theory, to a hyperfunction of the chromaffine tissue.

Porges has shown in dogs that extirpation of both adrenals causes a lowering of the amount of sugar in the blood and only a small amount of glycogen is to be found in the liver and muscle, although they were tested a few hours after the operation.[1]

We can produce hyperaction of the adrenals by injection of adrenalin. Then, as expected, we directly have rapid, excessive mobilization of the carbohydrates, and indirectly an inhibition of the pancreas function. By both ways we have glycosuria. As a further indirect result by the promotion of the thyroid, an increase

[1] *Berlin. Klin. Wochenschrift.* No. 25, p. 1187.

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in the metabolism of the proteids and fats.

In extirpation of the thyroid we have as a direct action the removal of the thyroid secretion, and hence a depression of the metabolism of the albumens, fats and inorganic salts, as an indirect action by the removal of the promotion of the thyroid on the chromaffine substance, a slower mobilization of the carbohydrates, and probably of the fats. Also by the want of the thyroid we find an absence of the intense inhibition of the thyroid on the pancreas; we have hyperfunction of pancreas, which explains why thyroidless dogs do not have glycosuria by injections of adrenalin.

In depancreatized dogs, by adrenalin injection, we have a secondary hyperfunction of the chromaffine tissue, hence an increased destruction of the proteids and fats, and the quotient of dextrose to nitrogen is raised. Here we have the mobilization of carbohydrates by adrenalin.

After removal of the thyroid and pancreas we have complicated relations.

The removal of the inhibition of the pancreas upon the chromaffine tissue is stronger than the removal of the promotion of thyroid on the chromaffine tissue, then hyperfunction of the chromaffine tissue is not so completely intense as after extirpation of the pancreas alone; hence, there is a probable heightened mobilization of fat. Hence, Falta gives the following explanation: the mobilization of fat is increased, the destruction of fat decreased, by the removal of

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thyroid, and a very slow decrease of body weight ensues, and in these circumstances we have sugar from fats and a heightened quotient of dextrose to nitrogen.

Relation of Internal Secretion to the Sympathetic and Parasympathetic System.—Loewi has shown by removal of the pancreas in dogs that dropping adrenalin into the eye causes mydriasis. It would seem that adrenalin in small doses does not act upon the normal eye, for the pancreas has an inhibitory effect upon the sympathetic nervous system. When the pancreas was removed the sympathetic became more excitable and adrenalin now acts, when normally it did not. In human diabetes the adrenalin action on the pupil is inconstant.

In hyperthyroidism by continued use of thyroid extract there seems to be an excitation of the sympathetic, as exophthalmos, tachycardia, tremor, sweat, and vaso-motor disturbances.

If a normal dog has thyroid extract fed to him, then adrenalin acts upon the pupil. It has been shown that in the normal thyroidless dogs continued use of thyroid made them susceptible to the action of adrenalin upon the pupil. Here the thyroid increased the activity of the sympathetic nervous system.

Iodothyrin also heightens the excitability of the sympathetic and adrenalin then acts upon the normal pupil. In about 20 cases of Basedow's disease the action of adrenalin only dilated the pupil in 4 cases.

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Hyperthyroidism also acts upon the parasympathetic as an excitant, as is shown in the well known antagonism between thyroid extract and atropin.

Athyreoidism conduces to lessened excitability of the sympathetic, for removal of the thyroid prevents the pressor action of small doses of adrenalin.

In thyroidless dogs Asber found that atropin acted more intensely than in normal, the sphincter is more easily paralyzed, since the excitation state of the parasympathetic fibers of the oculo motor is reduced. In thyroidless dogs pilocarpin has a diminished activity.

In myxedema, or hypothyroidism, we have a slow circulation, trophic disturbances and, perhaps, the slowness of the intestinal movements.

While adrenalin governs the sympathetic, Falta thinks the pancreas secretion may govern the vagus of the parasympathetic.

If the internal secretion of the pancreas governs the vagus, then irritation of the vagus must produce an increased production of the internal secretion of the pancreas, a hyperfunction of the pancreas, while a paralysis of the vagus is attended with a decrease of the pancreatic secretion. Suitable doses of pilocarpin prevents adrenalin glycosuria.

In thyroidless dogs where we have a hyperfunction of the pancreas, atropin diminishes this, and adrenalin again produces glycosuria.

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Action in Metabolism.—In these statements I shall rely mainly upon Falta[1] who has made experiments upon this subject. In the state of hunger, thyreoidin, adrenalin and infundibulin increase proteid metabolism. Pancreas and parathyroid inhibit proteid metabolism, as their removal increases it. As to carbohydrates, adrenalin and infundibulin increase their metabolism; pancreas and parathyroid inhibit it.

Thyreoidin accelerates fat metabolism; pancreas inhibits it.

Ingestion of thyroid tablets is followed by increased excretion by the intestine of phosphates; with the ingestion of the hypophysis a decrease of phosphates in urine and an increase of them in the fecal matter ensues.

Thyreoidin and infundibulin increase the excretion of calcium by the intestine and of magnesium by the urine. Osiris has shown that the excretion of phosphorus by the kidneys and intestines is exclusively dependent upon the calcium metabolism, hence thyreoidin increases the excretion of phosphorus. After the use of adrenalin the quotient $N : P_2O_3$ falls.

The parathyroids inhibit calcium excretion?

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while the calcium and sodium excreted is increased. Removal of pancreas and parathyroids markedly increases the excretion of chlorine in the urine during the state of hunger.

Infundibulin increases the excretion of uric acid. Here the increase of uric acid is due to oxidation of allantoin. Adrenalin increases the excretion of both uric acid and allantoin.

The continuous use of thyreoidin produces no atheroma of the arterial walls, while adrenalin and infundibulin cause it. In thyroidectomized dogs, infundibulin has less action on proteid metabolism. According to Diesing the pituitary contains a peculiar organic combination of phosphorus, the thyroid iodine, the spleen iron, the thymus arsenic, and the adrenals sulphur. These glands regulate the supply of these constituents in the blood for the acts of metabolism.

Secretion and Excretion.—In conjunction with Dr. Saml. B. Harris I have shown that adrenalin is excreted in small amounts by the kidney. The urine of cats who had received adrenalin a few hours previously was injected into jugular and a rise of arterial tension ensued. Normally the urine of the cat depresses the blood pressure. Dale has shown that pituitary is also excreted by the urine, as the urine of the cat after injection of the pituitary had a pressor action when tested on another cat.

Pemberton and Sweet have shown that the adrenals and pituitary inhibit the activity of the pancreatic secretion. This is not due to

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vaso-constriction in the gland vessels, as Edmunds held, but is independent of the systemic blood pressure. This action persists when the blood pressure is below normal. This inhibition by the pituitary and suprarenals ensues when the pancreas is stimulated by the action of hydrochloric acid in the duodenum.[1]

Parchtner, in a castrated male calf 11 months old, found a diminution of oxygen taken into the system from 12 to 15 per cent. He confirms Loewy and Richter's results.[2]

In castrated female dogs Loewy and Richter found that ovarian feeding elevated the amount of oxygen taken into the system by the lungs even above normal. Even in male castrated dogs öophorin increased the oxygen used up above normal, while in the non-castrate öophorin showed no increased using up of oxygen by the animal. In young animals castration causes a slow ossification and a slow calcification compared with non-castrates. In two cases of osteomalacia before castration there was a deficiency of 0.39, comparing the CaO ingested with the CaO excreted. After castration there was an excess of calcium +5.78 retained, comparing the calcium ingested with the calcium egested (Goldthwait, Painter, Osgood and MacCrudden[3]).

In a fat person Steyrer has shown in thyroid-

[1] *Archives of Internal Med.*, Vol. 5, No. 5, p. 466.

[2] Oppenheim's *Handbuch Biochemie*, Band 4, 2 Halfte, p. 201.

[3] *Ibid.*, p. 206.

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feeding that there was a fall of weight—the nitrogenized substances were spared but the fats were used up causing a minus balance of C, compared with carbon ingested.[1]

Secretory Nerves in the Thyroid.—Asher and Flack[2] have shown that on irritating the superior laryngeal nerve which dilates the blood vessels of the thyroid that there was an increased secretion of some substance by the thyroid which augments the excitability of the nervus depressor. During the irritation of the laryngeal nerves by electricity, the same dose of adrenalin elevates the blood pressure more if the depressors have been ligated previously. Von Cyon stated that iodothyrin excited the nervus depressor. Falta, by metabolism experiments, has shown that the adrenals and thyroid assist each other by their respective secretions.

I have indicated in the following table a provisional relation of some of the glands with an internal secretion upon each other.

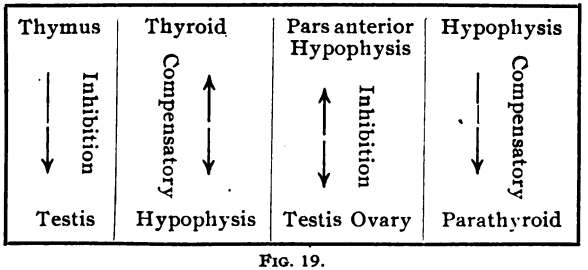

FIG. 19.

[1] Oppenheim's *Handbuch Biochemie*, Band 4, 2 Halfte, p. 234.
[2] *Zentralblatt für Physiologie Band*, XXIV, No. 6, p. 211.

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PATHOLOGY.

Deficiency of parathyroid secretion produces tetany.

Excess of secretion by thyroid produces Basedow's disease.

Deficiency of thyroid secretion produces in child cretinism, in adult myxedema.

Parhon[1] gives the following parallel of symptoms between Basedow's disease and mxyedema.

Basedow's disease.	*Myxedema.*
Frequent hypertrophy of thyroid gland.	Absence or frequent atrophy of thyroid.
Excess of sudorific secretion, skin smooth and moist.	Deficiency of sudorific secretion, skin dry, afterwards wrinkled.
Electric resistance diminished.	Electric resistance increased.
Sensation of heat, quite painful.	Continual sensation of cold.
Temperature of body frequently above normal.	Temperature of the body below normal.
Diarrhea frequent.	Constipation frequent.
Nutritive exchanges frequently exaggerated.	Nutritive exchanges diminished.
Growth accelerated.	Growth slow.
Enchondral ossification precocious.	Enchondral ossification retarded.
Irritability increased, psychic lability.	Psychic apathy.
Emotional instability.	

Henry J. Berkeley[2] has found that patients

[1] *Les Secretions Internes*, 1909.

[2] *Folia Neuro-biologica*, Nov., 1908, p. 157.

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with katatonia have their mental integrity restored by partial thyroidectomy.

In Basedow's disease, we have increased destruction of proteid. This augmented metabolism of proteid can be reduced to normal by large doses of carbohydrates and fats for some time. Carbohydrates and fats in the normal man reduces the metabolism of proteid.

In Basedow's disease, by giving large doses of sugar we can produce alimentary glycosuria. Quite often we have Basedow's disease and glycosuria combined. By the use of thyroid tablets we have occasional diabetes, probably due to a latent disposition to diabetes.

Diabetes can ensue from hyperfunction of thyroid, or excessive action of adrenalin. In some severe cases of diabetes in the young the thyroid could not be felt. Falta found in dogs with the thyroid and pancreas removed a strong diabetes. It is well known that disease of pancreas produces diabetes.

The diabetes which ensues during pregnancy in nervous cases and ends after delivery is very probably due to hyperhypophysy. The promotion of activity of the chromaffine tissue by the thyroid also is contributory.

Tumors of adrenals have been observed by Grawitz to produce diabetes, perhaps due to hyperactivity of the adrenals.

Deficiency of adrenalin produces Addison's disease.

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Hyperhypophysy produces in the child giantism, in the adult acromegaly.

Hypohypophysy produces dwarfs and infantilism.

Gross lesions of the pituitary have been found in at least four cases of *adiposis dolorosa*.

If ovarian insufficiency or thyroid insufficiency supervene before hyperhypophysy, then we have Dercum's disease.

Delille[1] makes the following symptoms for diseases of the hypophysis:

Hypohypophysy.	*Hyperhypophysy.*
Hypotension	Hypertension
Tachycardia	Polyuria
Painful sensations of heat	Glycosuria
Diminished quantity of urine	Emaciation
Anorexia	Obesity by an indirect action
Asthenia	Red blood corpuscles, normal or above normal
Nutrition changes, emaciation, in certain cases obesity	Acromegaly
Trophic troubles	Giantism
Psychic troubles	Psychic troubles
Insomnia	Sleepiness
Mental and physical backwardness	Nearly always genital insufficiency
Less resistance to infections	Frequent hypothyroidism
Signs of special intracranial compression by a tumor of pituitary	Signs of special intracranial compression by a tumor of pituitary

[1] *L'Hypophyse*, 1909.

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Strümpell thinks sclerodermia is due to hypohypophysy. Lafond confirms it. Leman and Van Wart suggest a hyperhypophysy and hypohypophysy of the anterior and posterior part of the pituitary, making thus four classifications of disease in this part.

Therapeutics.

In deficiency or loss of an internal secretion we substitute by giving the gland by the mouth. In excessive internal secretion of a gland we can overcome it by its antagonizing gland.

Bell and Schober have used the extract of the mammary gland in uterine myoma and obtained a diminution of the tumor and a cessation of the hemorrhages.

Mykertschianz[1] found mammin (Poehl), an extract of the mammary gland cause the disappearance of uterine fibroma in 2 cases a diminution of fibromas in 21 cases, and no action in 3 cases. The hemorrhage and pain were diminished. He also found mammin useful in chronic metritis.

The thyroid has been used to restrain metrorrhagia. It cures cretinism and myxedema. It also relieves obesity of pale people but not those with a high color.

Osteomalacia has been cured in many cases by ovarian castration.

Adrenalin has been locally applied to stop hemorrhages by its local vaso-constriction. It

[1] *Meunchener Med. Woch.*, Aug. 9, 1910, p. 1705.

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has also been used in congestions of the conjunctiva and of the nasal mucous membrane. It has been used in asthmas of cardiac and renal origin with good effect. Here the vasodilation of the coronary arteries and its tonic action on the cardiac muscle may come into play.

In bronchial asthma it has been applied locally to the nasal mucous membrane, and given internally. Internally it may act upon the broncho-constrictor muscles of the bronchi as an inhibitor, or as a stimulant upon the bronchodilators, or if there is congestion of the bronchial mucous membrane in these cases it would reduce the congestion.

It has been found after the removal of fluids from the pleural or peritoneal cavities that injection of adrenalin prevents its reaccumulation. In pneumonia of adults and children it has been used to prevent the debility of the muscular structure of the heart. In these cases it raises the peripheral resistance by the vaso-constriction and makes the left ventricle produce more work. Pulmonary edema in these states is not produced by its use.

In Addison's disease it improves but does not cure, as usually the lesions are of an incurable nature, being either tubercular or malignant. Used by the mouth in the lower animals in large doses it causes no perceptible increase of blood pressure. The surest way to its activity is subcutaneously, intramuscularly and intravenously. Adrenalin in patients with arterio-sclerosis and

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high blood pressure must be used with great care. Wiggers[1] has studied the effect upon internal hemorrhages, and has arrived at the conclusion that adrenalin increases the quantity of blood in the pulmonary veins as well as in the arteries, and that its use in pulmonary hemorrhage can not be looked upon as favorable. Small doses of adrenalin, according to Wiggers, that do not slow the heart generally cause no rise of pulmonary venous and arterial pressure, or only a feeble rise, even though the systemic pressure rises appreciably. Pressure measurements, however, give no accurate estimate of the blood contents of these vessels, for outflow records show that this is decidedly increased by adrenalin. This increase is not due, according to Wiggers, to a "back effect" from the systemic rise, for the pressure in the left auricle falls. It is not due to constriction of the pulmonary vessels, for the venous pressure should then fall and not rise. It is probably due to the fact that the total volume of blood thrown out by the augmented contraction of the right ventricle is not entirely forced ahead to be utilized in the feeding of the left heart, but instead is stored in the distensible pulmonary veins. Wiggers advises in intestinal hemorrhages not large doses, but small ones, 0.025 milligram, his so-called "therapeutic doses," which produce a rise of blood pressure and a diminished bleeding from the intestinal vessels. In these cases a high

[1] *Archives of Internal Medicine*, May, 1909.

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blood pressure should be avoided by a study of the rise by the spygmomanometer during the injections. In 1897, I showed that the adrenalin relaxed the intestine, which conduces to a checking of intestinal hemorrhage.

Heidenhain[1] found, as others have, that adrenalin in cases of collapse from weakness of the vasomotor center in pneumonia, diphtheria and peritonitis gave good results. It must be given subcutaneously or by the vein diluted with salt solution. He also used it in an apparently moribund case to tide him over an operation for ileus.

Kownatzki cured a patient afflicted with osteomalacia by adrenalin.[2]

I have referred to W. N. Berkeley's treatment of paralysis agitans by parathyroid extract.

Parhon and Urechia have tried the pituitary gland in paralysis agitans and have seen certain symptoms disappear, such as low arterial tension, tachycardia, the sensation of heat, increased perspiration, insomnia, and a diminution of the trembling. However, the rigidity was not modified.

Dr. A. F. Jaugeas has had good results from the X-rays, in tumors of the hypophysis and thinks they should be tried before any surgical operation is attempted.

Corpus luteum.—Maits[3] concludes from the

[1] *Journal Am. Med. Association*, p. 2100.

[2] *Berlin Klin. Wochenschrift*, No. 31, p. 1469.

[3] *University of Penna. Medical Bulletin*, Vol. XXIII, Nos. 5 and 6, p. 275.

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use of the extract of human corpus luteum that it has a distinct therapeutic action in osteomalacia in disturbances of the natural and artificial menopause and in hypofunction, due to infantile uterus.

Antidote.—Falta and Ivcovic[1] thought adrenalin was an antidote to strychnia, but Hans Januschke,[2] in repeating the experiments of Falta and Ivcovic, arrived at the following results:

(1) Adrenalin is not able to prevent the poisonous action of strychnia on the nervous system of the frog.

(2) Such adrenalin and strychnia mixtures which remain non-toxic by subcutaneous use in guinea pigs show typical strychnia poisoning by the intravenous use. The view of A. Exner, Meltzer and Auer, that there is a delay in the absorption of the poison in the lymphatics, receives support in his experiments.

(3) That the diastolic arrest of the frog's heart by strychnia can be caused to beat by adrenalin. This is not specific action but only an irritant action. Similar results can be produced by camphor, barium, strophanthin and atropin, also by mechanical and electrical irritation.

Olds[3] finds that thyroidectomized rats show the same resistance to morphine-poisoning as normal rats. He does not confirm Reid Hunt's results.

[1] *Berlin Klin. Wochenschrift*, 1909, p. 1929.
[2] *Wiener Klinische Wochenschrift*, 1910, p. 284.
[3] *Am. Journal of Physiology*, Vol. XXVI, p. 360.

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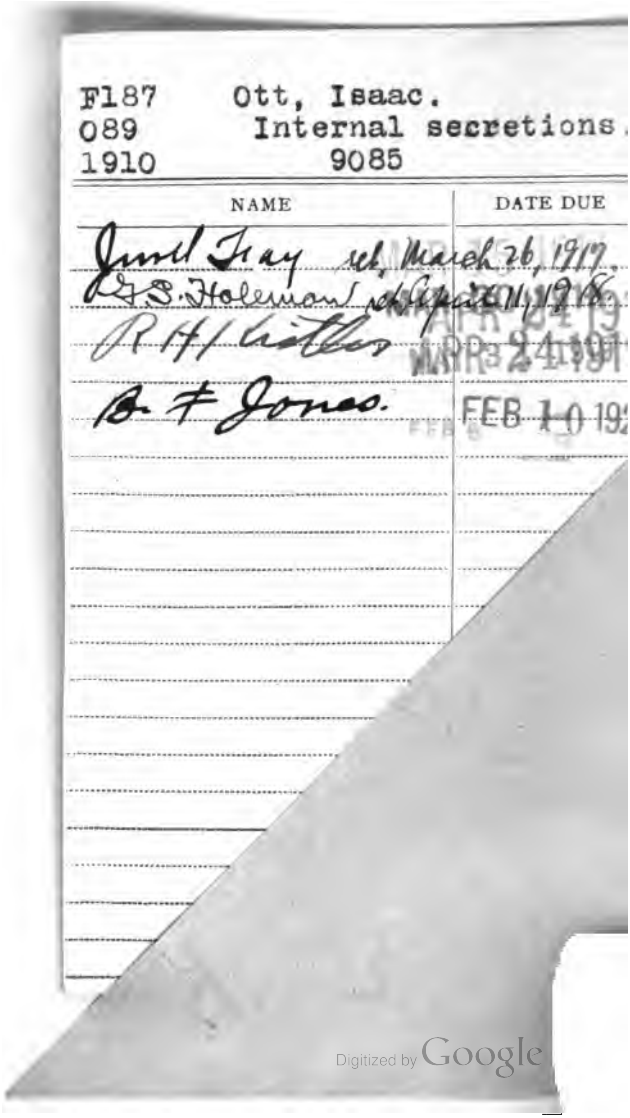

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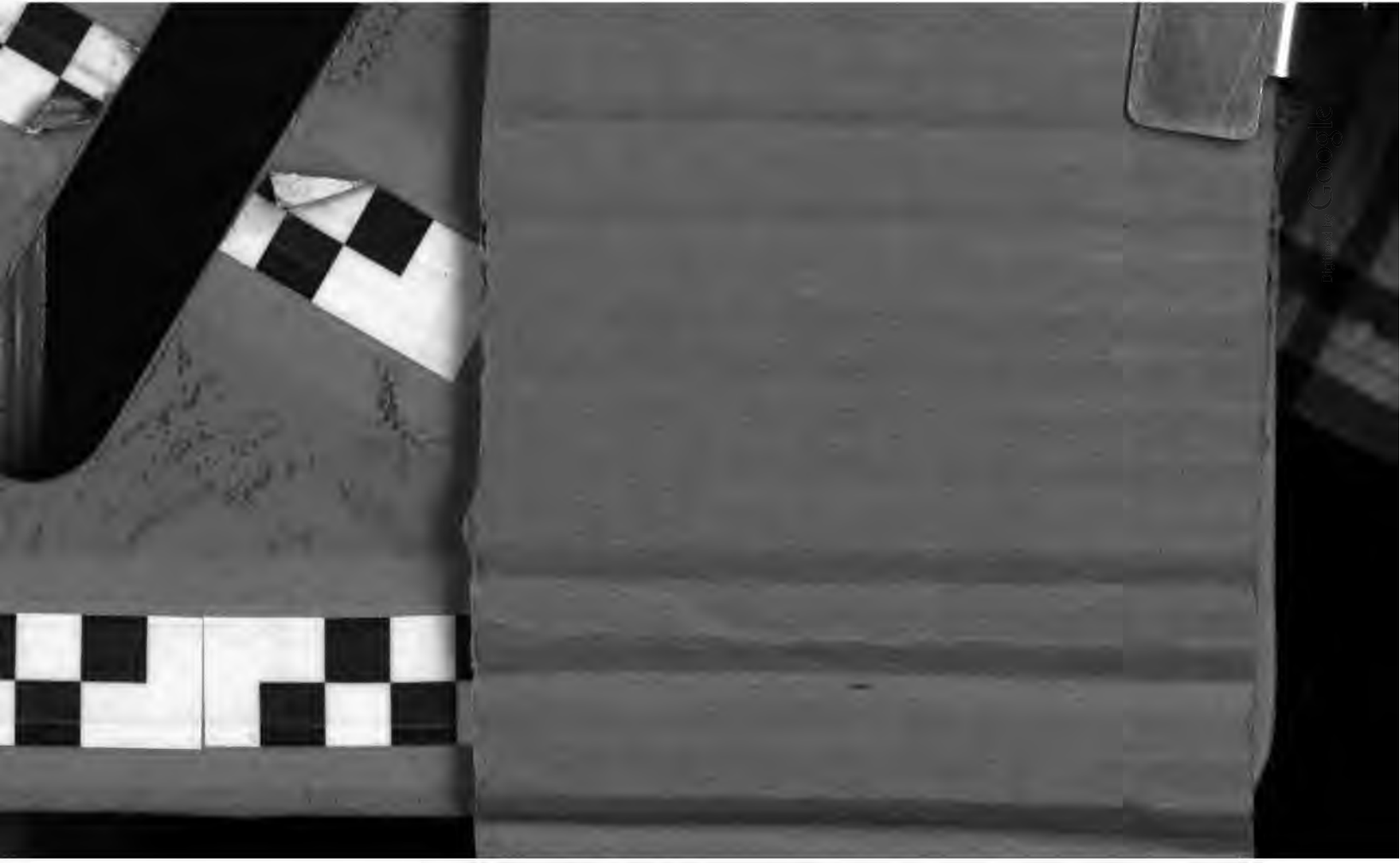

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